

PHARMACEUTICAL COMPOUNDS

This invention relates to 3-substituted tricyclic indazole compounds that inhibit or modulate the activity of cyclin dependent kinases (CDK), to the use of the
5 compounds in the treatment or prophylaxis of disease states or conditions mediated by cyclin dependent kinases, and to novel compounds having cyclin dependent kinase inhibitory or modulating activity. Also provided are pharmaceutical compositions containing the compounds and novel chemical intermediates.

Background of the Invention

- 10 Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Book. I and II*, Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine,
15 lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., *FASEB J.*, 9:576-596 (1995); Knighton, *et al.*, *Science*, 253:407-414 (1991); Hiles, *et al.*, *Cell*, 70:419-429 (1992); Kunz, *et al.*, *Cell*, 73:585-596 (1993); Garcia-Bustos, *et al.*, *EMBO J.*, 13:2352-2361 (1994)).
- 20 Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.
- 25 Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins

occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system, and angiogenesis.

The process of eukaryotic cell division may be broadly divided into a series of sequential phases termed G1, S, G2 and M. Correct progression through the various phases of the cell cycle has been shown to be critically dependent upon the spatial and temporal regulation of a family of proteins known as cyclin dependent kinases (CDKs) and a diverse set of their cognate protein partners termed cyclins. CDKs are cdc2 (also known as CDK1) homologous serine-threonine kinase proteins that are able to utilise ATP as a substrate in the phosphorylation of diverse polypeptides in a sequence dependent context. Cyclins are a family of proteins characterised by a homology region, containing approximately 100 amino acids, termed the "cyclin box" which is used in binding to, and defining selectivity for, specific CDK partner proteins.

Modulation of the expression levels, degradation rates, and activation levels of various CDKs and cyclins throughout the cell cycle leads to the cyclical formation of a series of CDK/cyclin complexes, in which the CDKs are enzymatically active. The formation of these complexes controls passage through discrete cell cycle checkpoints and thereby enables the process of cell division to continue. Failure to satisfy the pre-requisite biochemical criteria at a given cell cycle checkpoint, *i.e.* failure to form a required CDK/cyclin complex, can lead to cell cycle arrest and/or cellular apoptosis. Aberrant cellular proliferation, as manifested in cancer, can often be attributed to loss of correct cell cycle control. Inhibition of CDK

enzymatic activity therefore provides a means by which abnormally dividing cells can have their division arrested and/or be killed. The diversity of CDKs, and CDK complexes, and their critical roles in mediating the cell cycle, provides a broad spectrum of potential therapeutic targets selected on the basis of a defined biochemical rationale.

Progression from the G1 phase to the S phase of the cell cycle is primarily regulated by CDK2, CDK3, CDK4 and CDK6 via association with members of the D and E type cyclins. The D-type cyclins appear instrumental in enabling passage beyond the G1 restriction point, where as the CDK2/cyclin E complex is key to the transition from the G1 to S phase. Subsequent progression through S phase and entry into G2 is thought to require the CDK2/cyclin A complex. Both mitosis, and the G2 to M phase transition which triggers it, are regulated by complexes of CDK1 and the A and B type cyclins.

During G1 phase Retinoblastoma protein (Rb), and related pocket proteins such as p130, are substrates for CDK(2, 4, & 6)/cyclin complexes. Progression through G1 is in part facilitated by hyperphosphorylation, and thus inactivation, of Rb and p130 by the CDK(4/6)/cyclin-D complexes. Hyperphosphorylation of Rb and p130 causes the release of transcription factors, such as E2F, and thus the expression of genes necessary for progression through G1 and for entry into S-phase, such as the gene for cyclin E. Expression of cyclin E facilitates formation of the CDK2/cyclin E complex which amplifies, or maintains, E2F levels via further phosphorylation of Rb. The CDK2/cyclin E complex also phosphorylates other proteins necessary for DNA replication, such as NPAT, which has been implicated in histone biosynthesis. G1 progression and the G1/S transition are also regulated via the mitogen stimulated Myc pathway, which feeds into the CDK2/cyclin E pathway. CDK2 is also connected to the p53 mediated DNA damage response pathway via p53 regulation of p21 levels. p21 is a protein inhibitor of CDK2/cyclin E and is thus capable of blocking, or delaying, the G1/S transition. The CDK2/cyclin E complex may thus represent a point at which biochemical stimuli from the Rb, Myc and p53 pathways are to some degree

integrated. CDK2 and/or the CDK2/cyclin E complex therefore represent good targets for therapeutics designed at arresting, or recovering control of, the cell cycle in aberrantly dividing cells.

5 The exact role of CDK3 in the cell cycle is not clear. As yet no cognate cyclin partner has been identified, but a dominant negative form of CDK3 delayed cells in G1, thereby suggesting that CDK3 has a role in regulating the G1/S transition.

Although most CDKs have been implicated in regulation of the cell cycle there is evidence that certain members of the CDK family are involved in other biochemical processes. This is exemplified by CDK5 which is necessary for
10 correct neuronal development and which has also been implicated in the phosphorylation of several neuronal proteins such as Tau, NUDE-1, synapsin1, DARPP32 and the Munc18/Syntaxin1A complex. Neuronal CDK5 is conventionally activated by binding to the p35/p39 proteins. CDK5 activity can, however, be deregulated by the binding of p25, a truncated version of p35.
15 Conversion of p35 to p25, and subsequent deregulation of CDK5 activity, can be induced by ischemia, excitotoxicity, and β -amyloid peptide. Consequently p25 has been implicated in the pathogenesis of neurodegenerative diseases, such as Alzheimer's, and is therefore of interest as a target for therapeutics directed against these diseases.

20 CDK7 is a nuclear protein that has cdc2 CAK activity and binds to cyclin H. CDK7 has been identified as component of the TFIIH transcriptional complex which has RNA polymerase II C-terminal domain (CTD) activity. This has been associated with the regulation of HIV-1 transcription via a Tat-mediated biochemical pathway. CDK8 binds cyclin C and has been implicated in the
25 phosphorylation of the CTD of RNA polymerase II. Similarly the CDK9/cyclin-T1 complex (P-TEFb complex) has been implicated in elongation control of RNA polymerase II. PTEF-b is also required for activation of transcription of the HIV-1 genome by the viral transactivator Tat through its interaction with cyclin T1.

CDK7, CDK8, CDK9 and the P-TEFb complex are therefore potential targets for anti-viral therapeutics.

At a molecular level mediation of CDK/cyclin complex activity requires a series of stimulatory and inhibitory phosphorylation, or dephosphorylation, events. CDK phosphorylation is performed by a group of CDK activating kinases (CAKs) and/or
5 kinases such as wee1, Myt1 and Mik1. Dephosphorylation is performed by phosphatases such as cdc25(a & c), pp2a, or KAP.

CDK/cyclin complex activity may be further regulated by two families of endogenous cellular proteinaceous inhibitors: the Kip/Cip family, or the INK
10 family. The INK proteins specifically bind CDK4 and CDK6. p16^{ink4} (also known as MTS1) is a potential tumour suppressor gene that is mutated, or deleted, in a large number of primary cancers. The Kip/Cip family contains proteins such as p21^{Cip1, Waf1}, p27^{Kip1} and p57^{kip2}. As discussed previously p21 is induced by p53 and is able to inactivate the CDK2/cyclin(E/A) and CDK4/cyclin(D1/D2/D3)
15 complexes. Atypically low levels of p27 expression have been observed in breast, colon and prostate cancers. Conversely over expression of cyclin E in solid tumours has been shown to correlate with poor patient prognosis. Over expression of cyclin D1 has been associated with oesophageal, breast, squamous, and non-small cell lung carcinomas.

20 The pivotal roles of CDKs, and their associated proteins, in co-ordinating and driving the cell cycle in proliferating cells have been outlined above. Some of the biochemical pathways in which CDKs play a key role have also been described. The development of monotherapies for the treatment of proliferative disorders, such as cancers, using therapeutics targeted generically at CDKs, or at specific
25 CDKs, is therefore potentially highly desirable. CDK inhibitors could conceivably also be used to treat other conditions such as viral infections, autoimmune diseases and neuro-degenerative diseases, amongst others. CDK targeted therapeutics may also provide clinical benefits in the treatment of the previously described diseases when used in combination therapy with either existing, or new, therapeutic agents.
30 CDK targeted anticancer therapies could potentially have advantages over many

current antitumour agents as they would not directly interact with DNA and should therefore reduce the risk of secondary tumour development.

WO 02/34721 from Du Pont discloses a class of indeno [1,2-c]pyrazol-4-ones as inhibitors of cyclin dependent kinases.

- 5 WO 01/81348 from Bristol Myers Squibb describes the use of 5-thio-, sulfinyl- and sulfonylpyrazolo[3,4-b]-pyridines as cyclin dependent kinase inhibitors.

WO 00/62778 also from Bristol Myers Squibb discloses a class of protein tyrosine kinase inhibitors.

- 10 WO 01/72745A1 from Cyclacel describes 2-substituted 4-heteroaryl-pyrimidines and their preparation, pharmaceutical compositions containing them and their use as inhibitors of cyclin-dependant kinases (CDKs) and hence their use in the treatment of proliferative disorders such as cancer, leukaemia, psoriasis and the like.

- 15 WO 99/21845 from Agouron describes 4-aminothiazole derivatives for inhibiting cyclin-dependent kinases (CDKs), such as CDK1, CDK2, CDK4, and CDK6. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compositions containing such compounds and to methods of treating malignancies and other disorders by administering effective amounts of such compounds.

- 20 WO 01/53274 from Agouron discloses as CDK kinase inhibitors a class of compounds which can comprise an amide-substituted benzene ring linked to an N-containing heterocyclic group. Although indazole compounds are not mentioned generically, one of the exemplified compounds comprises an indazole 3-carboxylic acid anilide moiety linked via a methylsulfanyl group to a pyrazolopyrimidine.

- 25 WO 01/98290 (Pharmacia & Upjohn) discloses a class of 3-aminocarbonyl-2-carboxamido thiophene derivatives as protein kinase inhibitors. The compounds are stated to have multiple protein kinase activity.

US 3,705,175 and DE 2,135,398 (both to Egypt), disclose 6,7-dimethoxyindazole-3-carboxylic acid amides as anti-inflammatory and analgesic agents.

US 3,457,269 (Sterling Drug) discloses indazole-3-carboxylic acid amides, including anilides and pyridylamides, as hypotensive agents.

5 WO 01/53268 and WO 01/02369 from Agouron disclose compounds that mediate or inhibit cell proliferation through the inhibition of protein kinases such as cyclin dependent kinase or tyrosine kinase. The Agouron compounds have an aryl or heteroaryl ring attached directly or through a CH=CH or CH=N group to the 3-position of an indazole ring.

10 WO 02/10137 (Signal Pharmaceuticals) discloses a class of indazole derivatives as selective inhibitors of JNK kinase. The indazole derivatives have an aryl, heteroaryl or heterocyclic group linked to the indazole 3-position through an alkylene or alkenylene group.

US 6,340,685 (Scios) discloses a class of bicyclic heterocyclic compounds as
15 selective P38 MAP kinase inhibitors. Indazoles are not specifically disclosed.

WO 02/24635 (Fujisawa) discloses a class of amino alcohol derivatives as β -3 adrenergic receptor agonists. The compounds can contain an indazole 3-carboxylic acid anilide group linked to the amino alcohol group.

JP 01117882 (Dainippon) discloses a class of heterocyclic carboxamide derivatives
20 stated to be useful in treating certain gastrointestinal conditions.

WO 00/18738 (Zeneca) discloses a class of bis-arylamides that are p38 kinase inhibitors and inhibit the production of cytokines. No examples of indazoles are given.

WO 00/63215 (Sanofi-Synthelabo) describes various indazole carboxamides that
25 are useful as 5-HT₃ or 5-HT₄ antagonists. Some of the compounds disclosed have a third ring formed by a chain linking the indazole 1- and 7-positions.

WO 01/58869 (Bristol Myers Squibb) discloses a class of indazoles as cannabinoid receptor modulators.

WO 01/83472 (Acadia Pharmaceuticals) describes various bicyclic heterocyclic compounds, including indazole carboxamides, that have activity as muscarinic
5 agonists and are useful in the treatment of neurological disorders. No tricyclic indazole compounds are disclosed.

WO 96/02537 (SmithKline Beecham) discloses various heterocyclic carboxamide derivatives as 5HT_{2B/2C} antagonists. Indazoles are not specifically disclosed.

Summary of the Invention

10 The invention provides compounds that have cyclin dependent kinase inhibiting or modulating activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by the cyclin dependent kinases.

Accordingly, in one aspect, the invention provides novel compounds of the formula (I) as defined herein.

15 The invention also provides a compound of the formula (I) as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.

The invention also provides the use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a
20 disease state or condition mediated by a cyclin dependent kinase.

In a further aspect, the invention provides a method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

25 This invention also provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method

comprises administering to the mammal a compound of the formula (I) as defined herein in an amount effective in inhibiting abnormal cell growth.

This invention further provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method
 5 comprising administering to the mammal a compound of the formula (I) as defined herein in an amount effective to inhibit CDK2 activity.

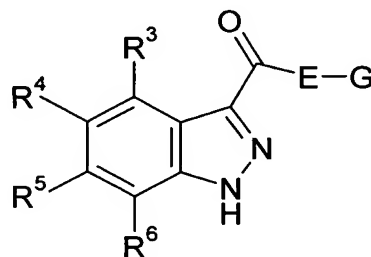
In another aspect, the invention provides a method of inhibiting a cyclin dependent kinase, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined herein.

10 The invention further provides a method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase using a compound of the formula (I) as defined herein.

In a further aspect, the invention provides a pharmaceutical composition comprising a novel compound of the formula (I) as hereinbefore defined and a
 15 pharmaceutically acceptable carrier.

The invention also provides compounds of the formula (I) for use in medicine.

The compounds of the invention are represented by the general formula (I):



(I)

20 wherein

E is O, S or NH;

G is selected from hydrogen; carbocyclic and heterocyclic groups having from 3 to 12 ring members; and acyclic C₁₋₈ hydrocarbyl groups optionally

substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the acyclic C₁₋₈ hydrocarbyl group may optionally be replaced by
 5 O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹; provided that E-G is not OH or SH and further provided that E-G does not contain the group O-O;

two adjacent moieties selected from R³, R⁴, R⁵ and R⁶, together with the carbon atoms to which they are attached, form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S;
 10 and the other two moieties selected from R³, R⁴, R⁵ and R⁶ are the same or different and are each selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, X¹C(X²), C(X²)X¹, X¹C(X²)X¹, S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from
 15 hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group
 20 may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹;

R^c is hydrogen or C₁₋₄ hydrocarbyl; and

X¹ is O, S or NR^c and X² is =O, =S or =NR^c.

References to “carbocyclic” and “heterocyclic” groups as used herein, either with
 25 regard to the group G or any other substituent group, unless the context indicates otherwise include both aromatic and non-aromatic ring systems. Thus, for example, the term “carbocyclic and heterocyclic groups having from 3 to 12 ring members” includes within its scope aromatic, non-aromatic, unsaturated, partially saturated and fully saturated carbocyclic and heterocyclic ring systems.

The carbocyclic or heterocyclic groups can be aryl or heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. The term “aryl” as used herein refers to a carbocyclic group having aromatic character and the term “heteroaryl” is used herein to denote a heterocyclic group having aromatic character. The terms “aryl” and “heteroaryl” embrace polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. In such polycyclic systems, the moiety E may be attached to the aromatic ring, or to a non-aromatic ring. The aryl or heteroaryl groups can be monocyclic or bicyclic groups and can be unsubstituted or substituted with one or more substituents, for example one or more groups R¹⁰ as defined below.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of a pyrazole, imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of heteroaryl groups include but are not limited to pyridyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, benzfuranyl, benzthiophenyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, isobenzofuranyl, isoindolyl, indoliziny, indolinyl, isoindolinyl, purinyl (e.g., adenine, guanine), indazolyl, benzodioxolyl,

chromenyl, isochromenyl, isochromanyl, benzodioxanyl, quinoliziny, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

5 Examples of polycyclic aryl and heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, dihydrobenzthienyl, dihydrobenzofuranyl, indolinyl and indanyl.

10 In the context of the group G, particular heteroaryl groups (whether attached directly to E or via a hydrocarbyl group) include monocyclic five or six-membered rings containing up to three heteroatoms (preferably up to two) selected from O, S and N. Presently preferred groups include imidazolyl, pyridyl and isoxazole.

Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

15 In the context of the group G, preferred aryl groups (whether attached directly to E or via a hydrocarbyl group) are groups based on a benzene ring. Thus it may be, for example, a phenyl group which is unsubstituted or has one or more substituents R¹⁰ as defined herein.

20 Examples of non-aromatic heterocyclic groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from nitrogen, oxygen and sulphur. The heterocyclic groups can contain, for example, cyclic ether moieties (e.g. as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene), cyclic amine moieties (e.g. as in
25 pyrrolidine), cyclic amides (such as a pyrrolidinone, piperidone or caprolactam), cyclic sulphonamides (such as an isothiazolidine 1,1-dioxide, [1,2]thiazinane 1,1-dioxide or [1,2]thiazepane 1,1-dioxide), cyclic sulphones (e.g. as in sulpholane and sulpholene)), cyclic sulfoxides, and combinations thereof.

Particular examples include morpholine, piperidine (e.g. 4-piperidinyl and 3-piperidinyl), pyrrolidine (e.g. 3-pyrrolidinyl and 2-pyrrolidinyl), pyrrolidone, tetrahydrofuran, tetrahydrothiophene, dioxan, tetrahydropyran (e.g. 4-tetrahydropyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, in the context of the group G, preferred non-aromatic heterocyclic groups include tetrahydropyran, morpholine, piperazine, piperidine and pyrrolidine.

Examples of non-aromatic carbocyclic groups include cycloalkane groups such as cyclohexyl and cyclopentyl.

The carbocyclic and heterocyclic groups can each be unsubstituted or substituted by one or more substituent groups R^{10} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2 , NR^c , SO_2NR^c or NR^cSO_2 ; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di- C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , NR^c , $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or = NR^c .

Where the substituent group R^{10} comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups R^{10} . In one sub-group of compounds of the formula (I), such further substituent groups R^{10} may include carbocyclic or heterocyclic groups, which are typically not themselves further substituted. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or

heterocyclic groups but are otherwise selected from the groups listed above in the definition of R¹⁰.

Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred.

- 5 In the definition of the compounds of the formula (I) above and as used hereinafter, the term “hydrocarbyl” is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. In certain cases, as defined herein, one or more of the carbon atoms making up the carbon backbone may be replaced by a specified atom or group of atoms.
- 10 Examples of such groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or substituted by one or more substituents as defined herein. The examples and preferences expressed below apply to each of the hydrocarbyl substituent groups or
- 15 hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the formula (I) unless the context indicates otherwise.

- Generally by way of example, the hydrocarbyl groups can have up to eight carbon atoms, unless the context requires otherwise. Within the sub-set of hydrocarbyl
- 20 groups having 1 to 8 carbon atoms, particular examples are C₁₋₆ hydrocarbyl groups, such as C₁₋₄ hydrocarbyl groups (e.g. C₁₋₃ hydrocarbyl groups or C₁₋₂ hydrocarbyl groups), specific examples being any individual value or combination of values selected from C₁, C₂, C₃, C₄, C₅, C₆, C₇ and C₈ hydrocarbyl groups.

- The term “alkyl” covers both straight chain and branched chain alkyl groups.
- 25 Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers. Within the sub-set of alkyl groups having 1 to 8 carbon atoms, particular examples are C₁₋₆ alkyl groups, such as C₁₋₄ alkyl groups (e.g. C₁₋₃ alkyl groups or C₁₋₂ alkyl groups).

Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Within the sub-set of cycloalkyl groups the cycloalkyl group will have from 3 to 8 carbon atoms, particular examples being C₃₋₆ cycloalkyl groups.

5 Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl. Within the sub-set of alkenyl groups the alkenyl group will have 2 to 8 carbon atoms, particular examples being C₂₋₆ alkenyl groups, such as C₂₋₄ alkenyl groups.

10 Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl. Within the sub-set of cycloalkenyl groups the cycloalkenyl groups have from 3 to 8 carbon atoms, and particular examples are C₃₋₆ cycloalkenyl groups.

15 Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups. Within the sub-set of alkynyl groups having 2 to 8 carbon atoms, particular examples are C₂₋₆ alkynyl groups, such as C₂₋₄ alkynyl groups.

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl.

20 Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

The definition "R^a-R^b" as used herein, either with regard to substituents present on the carbocyclic or heterocyclic moiety (e.g. as in the context of the group G), or with regard to other substituents present at other locations on the compounds of the
 25 formula (I), includes *inter alia* compounds wherein R^a is selected from a bond, O, CO, OC(O), SC(O), NR^cC(O), OC(S), SC(S), NR^cC(S), OC(NR^c), SC(NR^c), NR^cC(NR^c), C(O)O, C(O)S, C(O)NR^c, C(S)O, C(S)S, C(S)NR^c, C(NR^c)O, C(NR^c)S, C(NR^c)NR^c, OC(O)O, SC(O)O, NR^cC(O)O, OC(S)O, SC(S)O,

NR^cC(S)O, OC(NR^c)O, SC(NR^c)O, NR^cC(NR^c)O, OC(O)S, SC(O)S, NR^cC(O)S, OC(S)S, SC(S)S, NR^cC(S)S, OC(NR^c)S, SC(NR^c)S, NR^cC(NR^c)S, OC(O)NR^c, SC(O)NR^c, NR^cC(O)NR^c, OC(S)NR^c, SC(S)NR^c, NR^cC(S)NR^c, OC(NR^c)NR^c, SC(NR^c)NR^c, NR^cC(NR^cNR^c), S, SO, SO₂, NR^c, SO₂NR^c and NR^cSO₂ wherein R^c is as hereinbefore defined.

The moiety R^b can be hydrogen or it can be a group selected from carbocyclic and heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually from 5 to 10), and a C₁₋₈ hydrocarbyl group optionally substituted as hereinbefore defined.

Examples of hydrocarbyl, carbocyclic and heterocyclic groups are as set out above.

When present, a hydrocarbyl group can be optionally substituted by one or more substituents selected from hydroxy, oxo, alkoxy, carboxy, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, and monocyclic or bicyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members. Preferred substituents include halogen such as fluorine. Thus, for example, the substituent can be a partially fluorinated or perfluorinated group such as trifluoromethyl. In one embodiment preferred substituents include monocyclic carbocyclic and heterocyclic groups having 3-7 ring members.

Where an amino group has two hydrocarbyl substituents, they may, together with the nitrogen atom to which they are attached, and optionally with another heteroatom such as nitrogen, sulphur, or oxygen, link to form a ring structure of 4 to 7 ring members

One or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹ wherein X¹ and X² are as hereinbefore defined. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. Examples of groups in which a carbon atom of the hydrocarbyl group has been replaced by a replacement

atom or group as defined above include ethers and thioethers (C replaced by O or S), amides, esters, thioamides and thioesters (C replaced by $X^1C(X^2)$ or $C(X^2)X^1$), sulphones and sulfoxides (C replaced by SO or SO_2) and amines (C replaced by NR^c).

- 5 In the compounds of the formula (I), two adjacent moieties selected from R^3 , R^4 , R^5 and R^6 , together with the carbon atoms to which they are attached, form a fused heterocyclic group having from 5 to 7 ring members. Thus, for example, the fused heterocyclic group can be formed from the combination of R^3 and R^4 , or the combination of R^4 and R^5 , or the combination of R^5 and R^6 , together with their
 10 respective attached carbon atoms. In one preferred group of compounds, R^3 and R^4 together with the carbon atoms to which they are attached form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S.

- 15 The fused heterocyclic group can be aromatic or non-aromatic but preferably is aromatic.

Examples of fused heterocyclic rings include five and six membered rings such as thiazolo, isothiazolo, oxazolo, isoxazolo, pyrrolo, pyrido, thieno, furano, pyrimido, pyrazolo, pyrazino, and imidazolo fused rings. Five membered rings are preferred.

- 20 It is preferred that the fused heterocyclic group is selected from thiazolo, oxazolo, imidazolo and pyrido groups, one particularly preferred group being the thiazolo group.

- The fused heterocyclic group can be optionally substituted by one or more groups R^{10} as hereinbefore defined. In one embodiment, the substituents may be selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic
 25 carbocyclic and heterocyclic groups having from 3 to 7 (typically 5 or 6) ring members, a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2 , NR^c , SO_2NR^c or NR^cSO_2 ; and R^b is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more

substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di- C_{1-4} hydrocarbylamino, and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , NR^c , $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; and R^c , X^1 and X^2 are as hereinbefore defined.

- 5 Preferred substituents on the fused heterocyclic ring include amino, mono or di- C_{1-4} hydrocarbylamino, C_{1-4} hydrocarbyl optionally substituted by hydroxyl or amino, and N-linked monocyclic heterocyclic groups containing 1, 2 or 3 heteroatoms selected from N, O and S. Particular examples of substituents include amino, methylamino, ethylamino, cyclopropylamino, methyl, ethyl, hydroxymethyl, hydroxyethyl, N-pyrrolidinyl and N-imidazolyl.

- The other two groups selected from R^3 , R^4 , R^5 and R^6 that do not form part of the fused heterocyclic ring, are the same or different and are each selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 7 ring members; a group R^a - R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2 , NR^c , SO_2NR^c or NR^cSO_2 ; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di- C_{1-4} hydrocarbylamino, monocyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , NR^c , $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

- R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and
 X^1 is O, S or NR^c and X^2 is =O, =S or = NR^c .

- It is preferred that the other two groups R^3 to R^6 not forming part of the fused heterocyclic ring are selected from hydrogen and small substituents such as halogen, hydroxy, cyano, methyl, ethyl, cyclopropyl, trifluoromethyl, or amino. More preferably the said groups are selected from hydrogen, methyl, fluorine or chlorine, and most preferably they are each hydrogen.

The moiety E is selected from O, S and NH and is preferably O or NH, more preferably NH.

The group G is selected from hydrogen; carbocyclic and heterocyclic groups having from 3 to 12 ring members; and acyclic C₁₋₈ hydrocarbyl groups optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the acyclic C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹; provided that E-G is not OH or SH and further provided that E-G does not contain the group O-O.

In one embodiment of the invention, the group G can be a group of the formula A-B-R¹ as defined below.

When G is an optionally substituted hydrocarbyl group, it can be for example an optionally substituted C₁₋₆ hydrocarbyl group, e.g. a C₁₋₄ hydrocarbyl group, or a C₁₋₃ hydrocarbyl group or a C₁₋₂ hydrocarbyl group, particular examples being optionally substituted C₁, C₂ and C₃ hydrocarbyl groups.

In another embodiment, the group G can be selected from (CH₂)_m-R²-B-R¹, and (CH₂)_m-R¹ wherein m is 0 to 4, and R¹, R² and B are as defined below.

In a further embodiment, G is selected from hydrogen; monocyclic carbocyclic and heterocyclic groups having 5 or 6 ring members; and acyclic C₁₋₄ hydrocarbyl groups optionally substituted by one or more substituents selected from hydroxy, , halogen, amino, mono- or di-C₁₋₄ hydrocarbylamino, and monocyclic carbocyclic and heterocyclic groups having 5 or 6 ring members; provided that E-G is not OH or SH.

Particular examples of the group E-G are as shown in Table 1 below.

Table 1 -Examples of the Group E-G

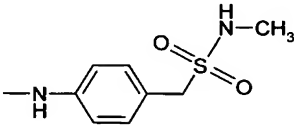
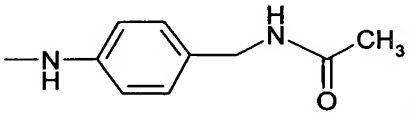
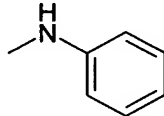
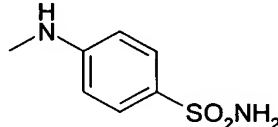
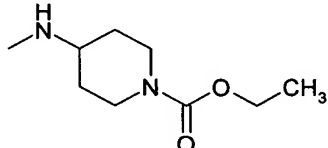
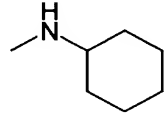
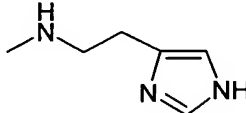
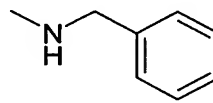
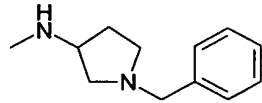
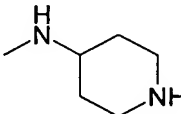
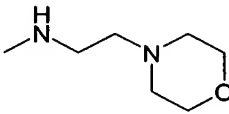
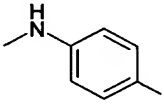
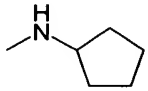
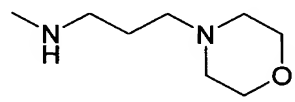
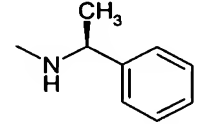
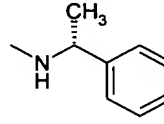
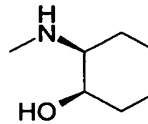
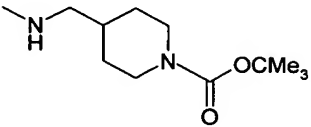
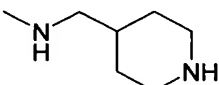
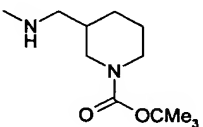
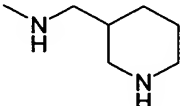
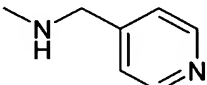
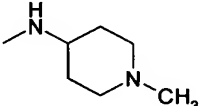
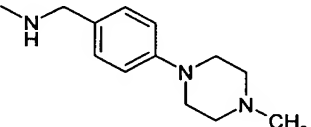
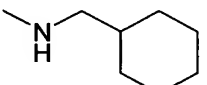
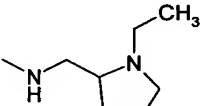
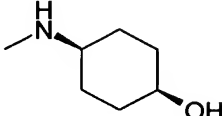
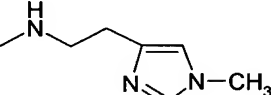
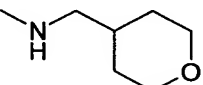
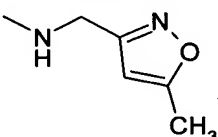
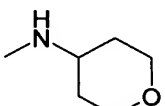
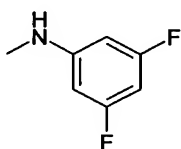

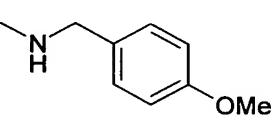
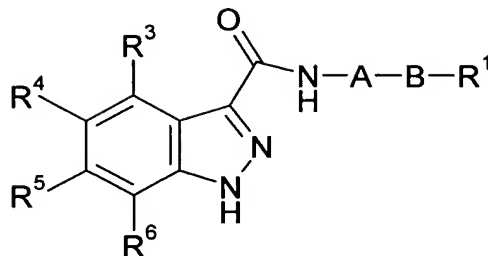
—O—CH_3 A	 B	 C
 D	 E	 F
 G	 H	 I
 J	 K	 L
 M	 N	 O
 P	 Q	 R

Table 1 -Examples of the Group E-G		
 S	 T	 U
 V	 W	 X
 Y	 Z	 AA
 AB	 AC	 AD
 AE	 AF	 AG
 AH	 AI	

One sub-group of compounds of the invention is represented by the general formula (II):



(II)

wherein

A is a group R^2 or CH_2-R^2 where R^2 is a carbocyclic or heterocyclic group
 5 having from 3 to 12 ring members;

B is a bond or an acyclic linker group having a linking chain length of up to
 3 atoms selected from C, N, S and O;

R^1 is hydrogen or a group selected from SO_2R^b , $SO_2NR^7R^8$, $CONR^7R^8$,
 NR^7R^9 and carbocyclic and heterocyclic groups having from 3 to 7 ring members;

10 R^3 and R^4 together with the carbon atoms to which they are attached form a
 fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring
 heteroatoms selected from N, O and S;

R^5 and R^6 are the same or different and are each selected from hydrogen,
 halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and
 15 heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a
 is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2 , NR^c , SO_2NR^c or
 NR^cSO_2 ; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups
 having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally
 substituted by one or more substituents selected from hydroxy, oxo, halogen,
 20 cyano, nitro, amino, mono- or di- C_{1-4} hydrocarbylamino, carbocyclic and
 heterocyclic groups having from 3 to 12 ring members and wherein one or more
 carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S,
 SO , SO_2 , NR^c , $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is hydrogen or C_{1-4} hydrocarbyl;

25 X^1 is O, S or NR^c and X^2 is =O, =S or = NR^c ;

R^7 is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally
 substituted by one or more substituents selected from hydroxy, oxo, halogen,

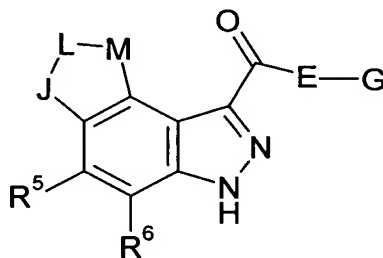
cyano, nitro, amino, mono- or di- C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , NR^c , $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

- 5 R^8 is selected from R^7 and carbocyclic and heterocyclic groups having from 3 to 12 ring members;

R^9 is selected from R^8 , COR^8 and SO_2R^8 ;

or NR^7R^8 or NR^7R^9 may each form a heterocyclic group having from 5 to 12 ring members.

- 10 Another sub-group of compounds of the invention is represented by the general formula (III):



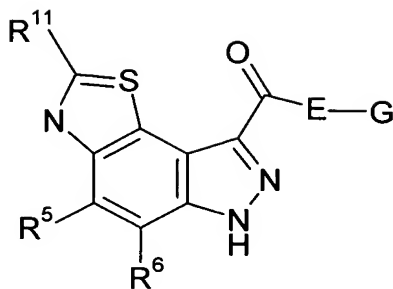
(III)

- 15 in which J, L and M are each independently selected from $=N-$, $-S-$, $-O-$ and $=CR^{11}$, R^{11} is hydrogen or a group R^{10} , and R^5 , R^6 , R^{10} , E and G are as hereinbefore defined.

It is preferred that at least one of J, L and M is other than a nitrogen atom.

It is further preferred that at least one of J, L and M is $=CR^{11}$.

- 20 Within the group of compounds defined by formula (III), a preferred sub-group of compounds is represented by the formula (IV):



(IV)

In the group of compounds of the formula (IV), R^5 and R^6 are preferably hydrogen or a small substituent selected from halogen, hydroxy, cyano, methyl, ethyl, trifluoromethyl, or amino, with hydrogen being particularly preferred.

Particular examples of compounds of the formula (IV) are compounds in which E-G is any one of the groups A to AI listed in Table 1 above.

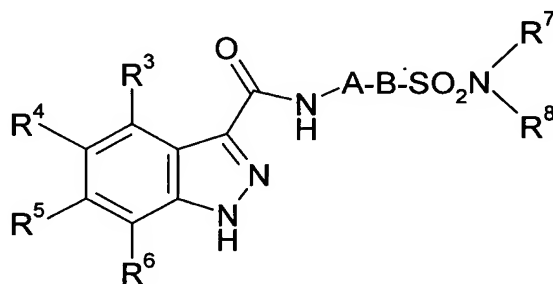
In the context of the formula (IV), examples of R^{11} include hydrogen and groups selected from halogen, hydroxy, trifluoromethyl, cyano, amino, mono- C_{1-4} alkylamino or di- C_{1-4} alkylamino, carbocyclic and heterocyclic groups having 5 to 7 ring members; and C_{1-4} hydrocarbyl groups optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, amino, and mono- or di- C_{1-4} hydrocarbylamino.

Particular groups R^{11} include, amino, mono- C_{1-4} alkylamino or di- C_{1-4} alkylamino, heterocyclic groups having 5 to 6 ring members and containing up to 2 heteroatoms selected from N, O and S; and C_{1-4} hydrocarbyl groups optionally substituted by one or more substituents selected from hydroxy, halogen, amino, and mono- or di- C_{1-4} hydrocarbylamino.

Specific examples of R^{11} include amino, methylamino, ethylamino, cyclopropylamino, methyl, ethyl, hydroxyethyl and pyrrolyl.

In another subgroup of compounds, R^5 and R^6 together with the carbon atoms to which they are attached form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S.

One sub-group of novel compounds of the invention is represented by the general
 5 formula (V):



(V)

wherein R^3 to R^8 , A and B are as hereinbefore defined.

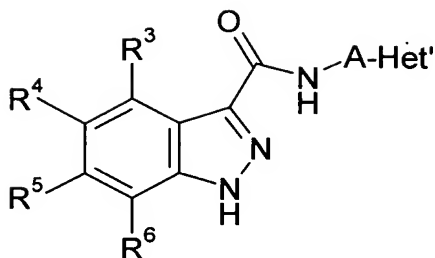
Within the sub-group of compounds of the formula (V), preferred compounds
 10 include those wherein A is a group R^2 wherein R^2 is an aryl group having six ring members and B is a bond or a methylene group.

Another preferred group of compounds within formula (V) is the group of
 compounds in which R^7 and R^8 are selected from hydrogen and C_{1-4} alkyl or R^7
 and R^8 together with the nitrogen atom form a saturated five or six membered
 15 heterocyclic ring having one or two heteroatoms.

Examples of such compounds include compounds wherein R^7 and R^8 together with
 the nitrogen atom form a saturated heterocyclic ring selected from morpholino,
 piperidino, piperazino and pyrrolidino.

Further particular examples are compounds in which R^7 is hydrogen and R^8 is
 20 hydrogen or methyl.

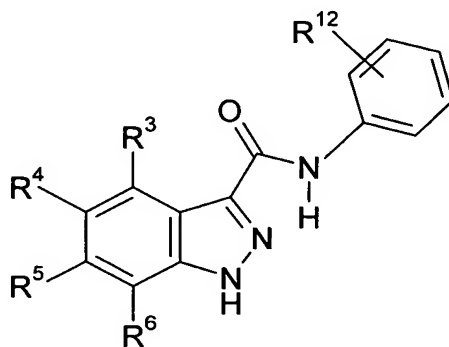
A further novel group of compounds of the invention is represented by the general
 formula (IV):



(VI)

wherein R^3 to R^6 and A are as hereinbefore defined and Het' is a heterocyclic group having from 3 to 7 ring members.

- 5 Another sub-group of novel compounds of the invention is represented by the formula (V):



(VII)

- 10 wherein R^3 to R^6 are as hereinbefore defined, and R^{12} represents hydrogen or one or more substituents selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl and trifluoromethoxy.

Particular examples of compounds of the formula (VII) are those in which R^{12} represents hydrogen or one or two fluorine atoms, preferably one fluorine atom.

- 15 In one general embodiment of the invention, the compounds of the formula (I) may be such that when A is R^2 and R^2 is an aryl group having 6 ring members and bearing a C_{1-6} alkyl or halogen substituent in the *para* position, the group B- R^1 is

other than an unsubstituted or substituted benzamido group located at the *meta* position of the aryl group.

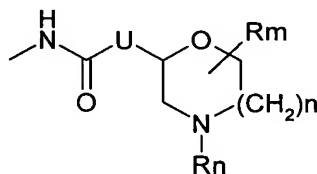
In another general embodiment, the compounds of the formula (I) may be such that
 5 when A is R² and R² is an aryl group having 6 ring members, the group B-R¹ is other than a substituted phenyl carbamoyl group located at the *meta* position of the aryl group wherein the substituted phenyl carbamoyl group bears a C₁₋₆ alkyl or halogen substituent in the *ortho* position and an amido group in the *para* position.

In another embodiment, the fused heterocyclic group, formed by two adjacent
 10 moieties selected from R³, R⁴, R⁵ and R⁶ together with the carbon atoms to which they are attached, is other than a 1,2,3-triazolo ring.

In a further general embodiment, the compound of the formula (I) is other than a compound containing a 3-aminocarbonyl-2-carboxamido-thiophene moiety.

In another general embodiment, when the compound of the formula (I) is one in
 15 which E is NH and G is an aryl or heteroaryl group selected from five or six membered heteroaryl groups, phenyl, quinolinyl and isoquinolinyl groups, the said aryl or heteroaryl group bears a substituent other than C₁₋₆ alkyl, halogen, CF₃, NR^xR^y and OR^z where R^x, R^y and R^z are independently hydrogen, C₁₋₆ alkyl or aryl-C₁₋₆ alkyl.

20 In another general embodiment, the group E-G is not a group of the formula:



wherein U is an alkylene group, Rm is hydrogen or an alkyl group, Rn is aryl, alkyl or arylalkyl and n is 1 or 2.

For the avoidance of doubt, it is to be understood that each general and specific
 25 preference, embodiment and example of the groups R¹ may be combined with each

general and specific preference, embodiment and example of the groups R^2 and/or R^3 and/or R^4 and/or R^5 and/or R^6 and/or E and/or G and that all such combinations are embraced by this application.

5 The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650, or less than 600, or less than 550. More preferably, the molecular weight is less than 525 and, for example, is 500 or less.

- 10 Specific novel compounds of the invention include:
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;
 - 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid [4-(acetylamino-methyl)-phenyl]-amide;
 - 15 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid phenylamide;
 - 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-sulfamoyl-phenyl)-amide;
 - 4-[(2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carbonyl)-amino]-
 - 20 piperidine-1-carboxylic acid ethyl ester;
 - 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid cyclohexylamide;
 - 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid [2-(1H-imidazol-4-yl)-ethyl]-amide;
 - 25 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid benzylamide;
 - 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid piperidin-4-ylamide;
 - 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (2-
 - 30 morpholin-4-yl-ethyl)-amide;

- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-fluorophenyl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid cyclopentylamide;
- 5 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (3-morpholin-4-yl-propyl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (2-hydroxy-cyclohexylmethyl)-amide;
- 4-[(2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carbonyl)-amino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester;
- 10 3-[(2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid piperidin-3-ylamide;
- 15 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (pyridin-4-ylmethyl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (1-methyl-piperidin-4-yl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid 4-(4-methyl-piperazin-1-yl)-benzylamide;
- 20 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid cyclohexylmethyl-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-hydroxy-cyclohexyl)-amide;
- 25 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid [2-(1-methyl-1H-imidazol-4-yl)-ethyl]-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (5-methyl-isoxazol-3-ylmethyl)-amide;
- 30

- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid
(tetrahydro-pyran-4-yl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (3,5-
difluoro-phenyl)-amide;
- 5 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid amide;
2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid 4-methoxy-
benzylamide;
- 2-ethylamino-6H-pyrazolo[4', 3':3, 4]benzo[1, 2-d]thiazole-8-carboxylic acid (4-
fluoro-phenyl)-amide;
- 10 2-Ethylamino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-
methylsulfamoylmethyl-phenyl)-amide;
- 2-Methyl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-fluoro-
phenyl)-amide;
- 2-Pyrrol-1-yl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-
15 fluoro-phenyl)-amide;
- 2-cyclopropylamino-6H-pyrazolo[4', 3': 3, 4]benzo[1, 2-d]thiazole-8-carboxylic
acid (4-fluoro-phenyl)-amide;
- 2-Hydroxymethyl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-
fluoro-phenyl)-amide;
- 20 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (1-benzyl-
pyrrolidin-3-yl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (1-phenyl-
ethyl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (1-phenyl-
25 ethyl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (piperidin-
4-ylmethyl)-amide;
- 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (1-ethyl-
pyrrolidin-2-ylmethyl)-amide; and
- 30 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (2-
hydroxy-1-phenyl-ethyl)-amide.

Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

If the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{3+} . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I).

Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide.

Where a compound contains several amine functions, one or more than one
 5 nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle.

N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic
 10 acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

15 Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by Formula (I). Examples of esters are compounds containing the group $-C(=O)OR$, wherein R is an ester substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group.
 20 Particular examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and $-C(=O)OPh$. Examples of acyloxy (reverse ester) groups are represented by $-OC(=O)R$, wherein R is an acyloxy substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group. Particular examples of acyloxy groups
 25 include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, $-OC(=O)Ph$, and $-OC(=O)CH_2Ph$.

Compounds of the formula may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of

several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

Also encompassed by formula (I) are any polymorphic forms of the compounds, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with
 5 compounds such as cyclodextrins, or complexes with metals) of the compounds, and pro-drugs of the compounds. By “prodrugs” is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).

For example, some prodrugs are esters of the active compound (e.g., a
 10 physiologically acceptable metabolically labile ester). During metabolism, the ester group ($-C(=O)OR$) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups ($-C(=O)OH$) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by
 15 deprotection if required.

Examples of such metabolically labile esters include those of the formula - $C(=O)OR$ wherein R is:

- C₁₋₇alkyl
 (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);
- 20 C₁₋₇aminoalkyl
 (e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and
 acyloxy-C₁₋₇alkyl
 (e.g., acyloxymethyl;
 acyloxyethyl;
- 25 pivaloyloxymethyl;
 acetoxymethyl;
 1-acetoxyethyl;
 1-(1-methoxy-1-methyl)ethyl-carboxyloxyethyl;
 1-(benzoyloxy)ethyl; isopropoxy-carboxyloxymethyl;
- 30 1-isopropoxy-carboxyloxyethyl; cyclohexyl-carboxyloxymethyl;

- 1-cyclohexyl-carbonyloxyethyl;
cyclohexyloxy-carbonyloxymethyl;
1-cyclohexyloxy-carbonyloxyethyl;
(4-tetrahydropyranyloxy) carbonyloxymethyl;
5 1-(4-tetrahydropyranyloxy)carbonyloxyethyl;
(4-tetrahydropyranyl)carbonyloxymethyl; and
1-(4-tetrahydropyranyl)carbonyloxyethyl).

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for
10 example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Where the compounds of the formula (I) contain chiral centres, all individual optical forms such as enantiomers, epimers and diastereoisomers, as well as
15 racemic mixtures of the compounds are within the scope of formula (I).

The compounds of the formula (I) are inhibitors of cyclin dependent kinases. As such, they are expected to be useful in providing a means of arresting, or recovering control of, the cell cycle in abnormally dividing cells. It is therefore anticipated that the compounds will prove useful in treating or preventing
20 proliferative disorders such as cancers. It is also envisaged that the compounds of the invention will be useful in treating conditions such as viral infections, autoimmune diseases and neurodegenerative diseases for example.

CDKs play a role in the regulation of the cell cycle, apoptosis, transcription, differentiation and CNS function. Therefore, CDK inhibitors could be useful in
25 the treatment of diseases in which there is a disorder of proliferation, apoptosis or differentiation such as cancer. In particular RB+ve tumours may be particularly sensitive to CDK inhibitors.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell

5 lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell

10 lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma, ; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or

15 schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratocanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

CDKs are also known to play a role in apoptosis, proliferation, differentiation and transcription and therefore CDK inhibitors could also be useful in the treatment of the following diseases other than cancer; viral infections, for example herpes virus,

20 pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus; cardiovascular diseases for example

25 cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia,

30 atherosclerosis, toxin-induced or alcohol related liver diseases, haematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases

of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

It has also been discovered that some cyclin-dependent kinase inhibitors can be used in combination with other anticancer agents. For example, the cytotoxic activity of cyclin-dependent kinase inhibitor flavopiridol, has been used with other anticancer agents in combination therapy.

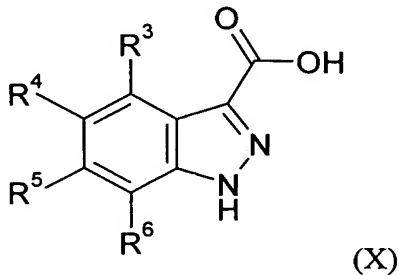
Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung carcinomas.

The activity of the compounds of the invention as inhibitors of cyclin dependent kinases can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC_{50} value. Preferred compounds of the present invention are compounds having an IC_{50} value of less than 1 micromole, more preferably less than 0.1 micromole.

Methods for the Preparation of Compounds of the Formula (I)

Compounds of the formula (I) in which E is NH can be prepared by reacting an amine of the formula H_2N-G with an indazole 3-carboxylic acid of the formula (X):



wherein R³ to R⁶ are as hereinbefore defined. The coupling reaction between the amine and the carboxylic acid (X) can be carried out by forming an activated derivative of the acid such as an acid chloride (e.g. by reaction with thionyl chloride), and then reacting the acid chloride with the amine, for example by the method described in *Zh. Obs. Khim.* 31, 201 (1961), and the method described in US 3,705,175.

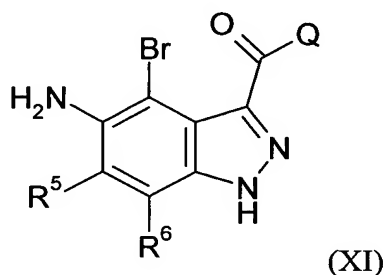
Alternatively, and more preferably, the coupling reaction between the carboxylic acid (X) and the amine can be carried out in the presence of an amide coupling reagent of the type commonly used to form peptide linkages. Examples of such reagents include 1,3-dicyclohexylcarbodiimide (DCC) (Sheehan *et al*, *J. Amer. Chem Soc.* 1955, 77, 1067), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDC) (Sheehan *et al*, *J. Org. Chem.*, 1961, 26, 2525), uronium-based coupling agents such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (L. A. Carpino, *J. Amer. Chem. Soc.*, 1993, 115, 4397) and phosphonium-based coupling agents such as 1-benzotriazolyloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) (Castro *et al*, *Tetrahedron Letters*, 1990, 31, 205). Carbodiimide-based coupling agents are advantageously used in combination with 1-hydroxy-benzotriazole (HOBt) (Konig *et al*, *Chem. Ber.*, 103, 708, 2024-2034). Preferred coupling reagents include EDC and DCC in combination with HOBt.

The coupling reaction is typically carried out in a non-aqueous, non-protic solvent such as dichloromethane, dimethylformamide or *N*-methylpyrrolidine. The reaction can be carried out at room temperature or, where the reactants are less reactive (for example in the case of electron-poor anilines bearing electron withdrawing groups such as sulphonamide groups) at an appropriately elevated temperature. The reaction may be carried out in the presence of a non-interfering base, for example a tertiary amine such as triethylamine or *N,N*-diisopropylethylamine.

Indazole carboxylic acids of the formula (X) can be prepared by hydrolysis of the corresponding esters (for example the ethyl or methyl esters) using an alkaline

metal hydroxide such as lithium hydroxide in accordance with standard methods. The esters can be prepared by a variety of routes using known synthetic chemical methods and readily available reagents. For example, esters of indazole carboxylic acids of the formula (X) in which R^3 and R^4 together with their attached carbon atoms form a thiazole ring can be prepared using the methods described below.

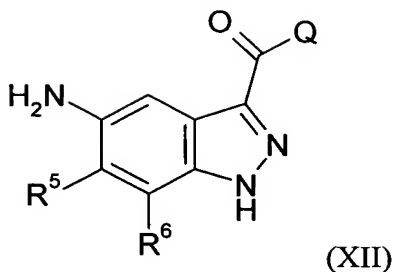
As an alternative to coupling a carboxylic acid with a compound of the formula NH_2-G , the tricyclic indazole compounds of the invention can be prepared by annulation of an appropriately substituted bicyclic indazole compound. Thus, for example, compounds of the formula (IV) above, wherein R^3 and R^4 together with their attached carbon atoms form a thiazole ring, in which the substituent R^{11} is an amino group, can be prepared from 5-amino-4-bromo-1H-indazoles of the formula (XI):



wherein Q is a group $NH-G$ or $O-G$ and R^5 , R^6 and G are as hereinbefore defined.

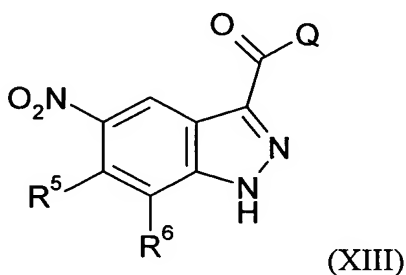
The compound of the formula (XI) can be reacted with an appropriately substituted isothiocyanate (e.g. an alkyl, aralkyl or cycloalkyl substituted isothiocyanate such as ethyl isothiocyanate or cyclopropyl isothiocyanate) to give the substituted amino thiazolo compound. The reaction can be carried out in a polar solvent such as methanol with heating, for example to a temperature of up to about $120^{\circ}C$. The reaction may conveniently be effected using microwave heating.

Compounds of the formula (XI) can be prepared by bromination of an amino compound of the formula (XII):

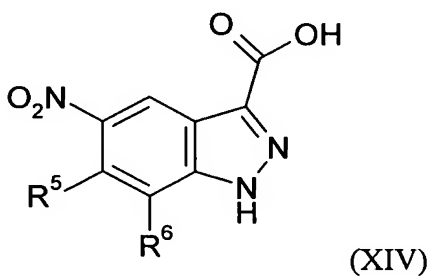


Bromination can be effected under mild conditions using either Br₂, or a brominating agent such as N-bromosuccinimide in the presence of an acid such as sulphuric acid. The reaction is typically carried out at a reduced temperature such as -5°C to 0°C in a polar water-miscible solvent such as methanol or tetrahydrofuran.

The amines of formula (XII) can be prepared from the corresponding nitro-compound of the formula (XIII) by reduction with a suitable reducing agent. Typical reduction conditions include catalytic reduction with hydrogen over palladium on charcoal.



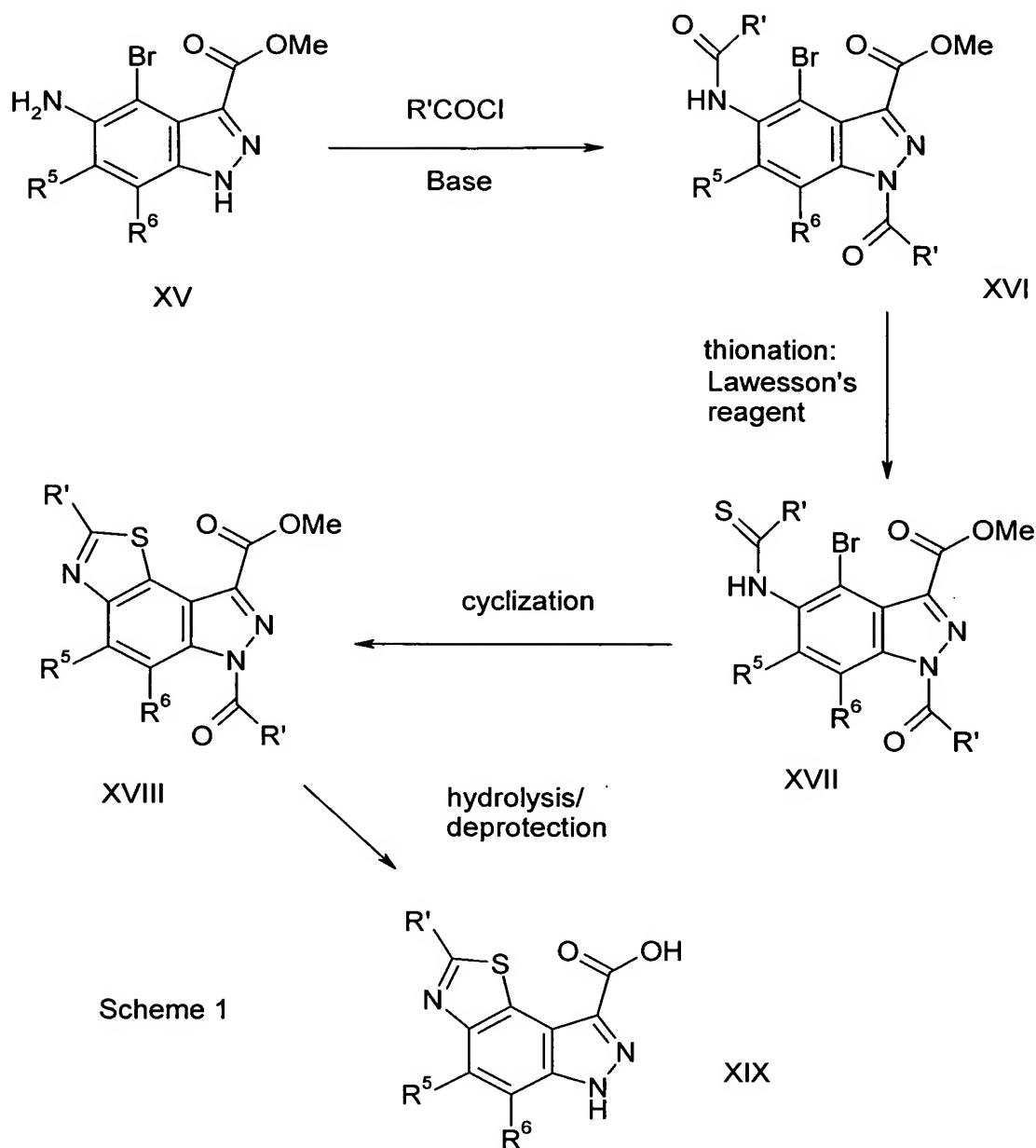
The nitro-compounds can be prepared from the corresponding 5-nitro-indazole carboxylic acid of the formula (XIV):



Where the compound of the formula (XIII) is an amide in which Q is a group NH-G, the carboxylic acid (XIV) can be reacted with a compound of the formula (G-NH₂) under the amide coupling conditions described above. Where the compound of the formula (XIII) is an ester in which Q is a group O-G, the carboxylic acid can
5 be reacted with a hydroxy compound (e.g. an alcohol) of the formula HO-G (e.g. an alkanol such as ethanol or methanol) under standard esterification conditions, for example by heating a solution of the carboxylic acid and the hydroxyl compound in the presence of an acid catalyst such as hydrochloric acid.

The nitro-compounds of the formula (XIV) can be obtained commercially or can
10 be prepared by nitration of the corresponding indazole compound having a hydrogen atom at the 5-position. Nitration can be effected under standard conditions well known to the skilled person, for example using a mixture of potassium nitrate and concentrated sulphuric acid at a temperature between about 0°C and room temperature, with ice cooling where necessary upon addition of the
15 nitrating mixture to the indazole compound.

Thiazolo-indazole compounds of the formula (IV), in which the substituent group R¹¹ is an optionally substituted hydrocarbyl group, can be prepared by reacting a carboxylic acid of the formula (XIX) below with an amine of the formula H₂N-G using the amide coupling procedures described above. The carboxylic acid (XIX)
20 can be prepared by a series of reactions starting from a carboxylic acid ester of the formula (XV) as shown in Scheme 1 below.

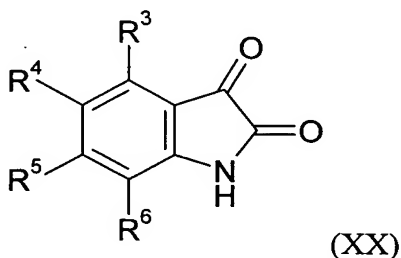


The amine (XV) can be reacted with an acylating agent for introducing the group $R'CO$ where R' is an optionally substituted hydrocarbyl group falling within the definition of R^{11} above. Where necessary, substituents such as hydroxyl groups present in R' can be protected by means of a suitable protecting group, for example in the form of esters. The acylating agent, which can be an acyl chloride, is reacted with the compound of formula (XV) in the presence of an organic base, typically a

tertiary amine such as triethylamine, usually at a reduced temperature, for example at a temperature of -78°C .

The oxygen atom of the carbonyl group of the primary amido group is then replaced with sulphur using a thionating reagent such as Lawesson's reagent ((H. Zechner *et al.* J. Amer. Chem. Soc. 78, 5018 (1956) and M.P Cava *et al.* Tetrahedron, 41, 5061-5087 (1985)) and heated to bring about cyclization to the triazolo-indazole (XIX).

Tricyclic indazole carboxylic acids of the formula (X) above can be prepared by annulation of a suitably substituted bicyclic carboxylic acid or ester derivative thereof, for example using the synthetic methods set out above in, for example, scheme 1. Substituted bicyclic indazole carboxylic acids can be prepared from compounds of the formula (XX):



by a sequence of reactions involving ring-opening, diazotisation, reduction and cyclisation. Ring opening of the substituted isatin analogue to give an *ortho*-amino-glyoxylic acid derivative can be achieved using an aqueous alkali such as sodium hydroxide with moderate heating, for example to a temperature of 35°C . The amine can then be converted to the diazonium salt by treatment with nitrous acid (for example generated from sodium nitrite and sulphuric acid) at a reduced temperature (e.g. approximately 5°C). The diazonium salt is reduced to form a hydrazine using a reducing agent such as tin (II) chloride and is then cyclised to the indazole by a cyclo-condensation reaction.

Isatin analogues of the formula (XX) can be prepared by a variety of known methods.

For example, according to the method described by Hewawasam *et al*, *Tetrahedron Letters*, 1994, 35, 7303-7306, an N-protected aminobenzene ring can be subjected to *ortho*-lithiation and the lithiated intermediate reacted with diethyl oxalate to give an α -ketoester which cyclises to give an isatin analogue upon deprotection of the amino group.

According to the method of Garden *et al*, *Tetrahedron Letters*, 1997, 38, 1501-1504, a substituted aminobenzene ring can be reacted with trichloroacetaldehyde and hydroxylamine in the presence of acid to give an α -isonitrosoacetyl amino benzene ring which cyclises to give an isatin analogue.

According to the method of Kraynack *et al*, *Tetrahedron Letters*, 1998, 39, 7679-7682, substituted isatin analogues can be formed by the γ -dibromination of the corresponding tricyclic 2-oxo-indoline derivative and subsequent hydrolysis of the resulting dibromo-compounds.

Substituted indazole 3-carboxylic acids that may be used as the starting materials for annulation procedures to give tricyclic indazole carboxylic acids are described in H. Harada *et al*, *Chem. Pharm. Bull.*, 43(11), 1912-1930 (1995). Further examples of synthetic procedures for making substituted indazole 3-carboxylic acids and esters can be found in WO 01/58869 (Bristol Myers Squibb).

Compounds of the formula (I) can also be prepared from other compounds of the formula (I) bearing suitable substituents and suitable reactive groups. For example, compounds wherein one or more of R^3 to R^6 are bromine or iodine, particularly iodine, can be used as intermediates for the preparation of other compounds of the formula (I). Compounds in which one or more of R^3 to R^6 are amine groups can be used to prepare N-linked heterocyclic substituents such as pyrrolyl groups, and groups consisting of or containing amino or hydroxyl groups can be converted to amides, esters and ethers according to standard methods.

Other examples of functional group interconversions can be found in *Fiesers' Reagents for Organic Synthesis*, Volumes 1-17, John Wiley, edited by Mary Fieser

(ISBN: 0-471-58283-2), and *Organic Syntheses*, Volumes 1-8, John Wiley, edited by Jeremiah P. Freeman (ISBN: 0-471-31192-8), 1995.

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999). A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃, -OAc). An aldehyde or ketone group may be protected, for example, as an acetal (R-CH(OR)₂) or ketal (R₂C(OR)₂), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C(OR)₂), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid. An amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH₃); a benzyloxy amide (-NHCO-OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH₃)₃, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), or as a 2-(phenylsulphonyl)ethyloxy amide (-NH-Psec). Other protecting groups for amines, such as cyclic amines and heterocyclic N-H groups, include toluenesulphonyl (tosyl) and methanesulphonyl (mesyl) groups and benzyl groups such as a *para*-methoxybenzyl (PMB) group. A carboxylic acid group may be protected as an ester for example, as: an C₁₋₇ alkyl ester (e.g., a methyl ester; a t-butyl ester); a C₁₋₇ haloalkyl ester (e.g., a C₁₋₇ trihaloalkyl ester); a triC₁₋₇ alkylsilyl-C₁₋₇alkyl ester; or a C₅₋₂₀ aryl-C₁₋₇ alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide. A thiol group may be

protected, for example, as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

A more detailed description of the processes that can be used to prepare the compounds of the formula (I) can be found in the specific examples set out below.

- 5 Chemical intermediates of the formulae (X) to (XX) represent a further aspect of the invention.

Pharmaceutical Formulations

The invention also provides compounds of the formula (I) as hereinbefore defined in the form of pharmaceutical compositions.

- 10 The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by
15 injection, infusion or other means of delivery.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

- Pharmaceutical compositions containing compounds of the formula (I) can be
20 formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

- Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium
25 carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard

ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit TM type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. As a further alternative, the active compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations may be prepared in accordance with methods well known to those skilled in the art.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

5 Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

10 Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

15 Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administered in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

20 The compounds of the inventions will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 0.1 milligrams to 2 grams of active ingredient, more usually from 10 milligrams to 1 gram, for example, 50 milligrams to 500 milligrams.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

25 **Methods of Treatment**

It is envisaged that the compounds of the formula (I) will be useful in the prophylaxis or treatment of a range of disease states or conditions mediated by cyclin

dependent kinases. Examples of such disease states and conditions are set out above.

Compounds of the formula (I) are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.

- 5 The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to
10 administer compounds in amounts that are associated with a degree of toxicity.

- A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 10 milligrams per kilogram of bodyweight although higher or lower doses may be administered where required. Ultimately, the quantity of compound administered
15 will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

- The compounds of the formula (I) can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic
20 disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include cytotoxic agents, agents that prevent cell proliferation or radiotherapy. Examples of such agents include but are not limited to topoisomerase inhibitors, alkylating agents, antimetabolites,
25 DNA binders and microtubule inhibitors, such as cisplatin, cyclophosphamide, doxorubicin, irinotecan, fludarabine, 5FU, taxanes and mitomycin C.

Antifungal Use

In a further aspect, the invention provides the use of the compounds of the formula (I) as hereinbefore defined as antifungal agents.

5 The compounds of the formula (I) may be used in animal medicine (for example in the treatment of mammals such as humans), or in the treatment of plants (e.g. in agriculture and horticulture), or as general antifungal agents, for example as preservatives and disinfectants.

10 In one embodiment, the invention provides a compound of the formula (I) as hereinbefore defined for use in the prophylaxis or treatment of a fungal infection in a mammal such as a human.

Also provided is the use of a compound of the formula (I) for the manufacture of a medicament for use in the prophylaxis or treatment of a fungal infection in a mammal such as a human.

15 For example, compounds of the invention may be administered to human patients suffering from, or at risk of infection by, topical fungal infections caused by among other organisms, species of *Candida*, *Trichophyton*, *Microsporum* or *Epidermophyton*, or in mucosal infections caused by *Candida albicans* (e.g. thrush and vaginal candidiasis). The compounds of the invention can also be administered for the treatment or prophylaxis of systemic fungal infections caused by, for
20 example, *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Coccidioides*, *Paracoccidioides*, *Histoplasma* or *Blastomyces*.

25 In another aspect, the invention provides an antifungal composition for agricultural (including horticultural) use, comprising a compound of the formula (I) together with an agriculturally acceptable diluent or carrier.

The invention further provides a method of treating an animal (including a mammal such as a human), plant or seed having a fungal infection, which

comprises treating said animal, plant or seed, or the locus of said plant or seed, with an effective amount of a compound of the formula (I).

The invention also provides a method of treating a fungal infection in a plant or seed which comprises treating the plant or seed with an antifungally effective
5 amount of a fungicidal composition as hereinbefore defined.

Differential screening assays may be used to select for those compounds of the present invention with specificity for non-human CDK enzymes. Compounds which act specifically on the CDK enzymes of eukaryotic pathogens can be used as anti-fungal or anti-parasitic agents. Inhibitors of the *Candida* CDK kinase, CKSI,
10 can be used in the treatment of candidiasis. Antifungal agents can be used against infections of the type hereinbefore defined, or opportunistic infections that commonly occur in debilitated and immunosuppressed patients such as patients with leukemias and lymphomas, people who are receiving immunosuppressive therapy, and patients with predisposing conditions such as diabetes mellitus or
15 AIDS, as well as for non-immunosuppressed patients.

Assays described in the art can be used to screen for agents which may be useful for inhibiting at least one fungus implicated in mycosis such as candidiasis, aspergillosis, mucormycosis, blastomycosis, geotrichosis, cryptococcosis, chromoblastomycosis, coccidioidomycosis, conidiosporosis, histoplasmosis,
20 maduromycosis, rhinosporidiosis, nocardiosis, para-actinomycosis, penicilliosis, monoliasis, or sporotrichosis. The differential screening assays can be used to identify anti-fungal agents which may have therapeutic value in the treatment of aspergillosis by making use of the CDK genes cloned from yeast such as *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus nidulans*,
25 or *Aspergillus terreus*, or where the mycotic infection is mucormycosis, the CDK assay can be derived from yeast such as *Rhizopus arrhizus*, *Rhizopus oryzae*, *Absidia corymbifera*, *Absidia ramosa*, or *Mucor pusillus*. Sources of other CDK enzymes include the pathogen *Pneumocystis carinii*.

By way of example, *in vitro* evaluation of the antifungal activity of the compounds can be performed by determining the minimum inhibitory concentration (M.I.C.) which is the concentration of the test compounds, in a suitable medium, at which growth of the particular microorganism fails to occur. In practice, a series of agar
5 plates, each having the test compound incorporated at a particular concentration is inoculated with a standard culture of, for example, *Candida albicans* and each plate is then incubated for an appropriate period at 37 °C. The plates are then examined for the presence or absence of growth of the fungus and the appropriate M.I.C. value is noted

- 10 The *in vivo* evaluation of the compounds can be carried out at a series of dose levels by intraperitoneal or intravenous injection or by oral administration, to mice that have been inoculated with a fungus, e.g., a strain of *Candida albicans* or *Aspergillus flavus*. The activity of the compounds can be assessed on the basis of the survival of a treated group of mice after the death of an untreated group of
15 mice. The activity may be measured in terms of the dose level at which the compound provides 50% protection against the lethal effect of the infection (PD₅₀).

For human antifungal use, the compounds of the formula (I) can be administered alone or in admixture with a pharmaceutical carrier selected in accordance with the intended route of administration and standard pharmaceutical practice. Thus, for
20 example, they may be administered orally, parenterally, intravenously, intramuscularly or subcutaneously by means of the formulations described above in the section headed "Pharmaceutical Formulations".

For oral and parenteral administration to human patients, the daily dosage level of the antifungal compounds of the formula (I) be from 0.01 to 10 mg/kg (in divided
25 doses), depending on *inter alia* the potency of the compounds when administered by either the oral or parenteral route. Tablets or capsules of the compounds may contain, for example, from 5 mg. to 0.5 g of active compound for administration singly or two or more at a time as appropriate. The physician in any event will determine the actual dosage (effective amount) which will be most suitable for an

individual patient and it will vary with the age, weight and response of the particular patient.

Alternatively, the antifungal compounds of formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they can be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

- 10 In addition to the therapeutic uses described above, anti-fungal agents developed with such differential screening assays can be used, for example, as preservatives in foodstuff, feed supplement for promoting weight gain in livestock, or in disinfectant formulations for treatment of non-living matter, e.g., for decontaminating hospital equipment and rooms. In similar fashion, side by side comparison of inhibition of a mammalian CDK and an insect CDK, such as the *Drosophila* CDK5 gene (Hellmich et al. (1994) FEBS Lett 356:317-21), will permit selection amongst the compounds herein of inhibitors which discriminate between the human/mammalian and insect enzymes. Accordingly, the present invention expressly contemplates the use and formulations of the compounds of the invention in insecticides, such as for use in management of insects like the fruit fly.

- In yet another embodiment, certain of the subject CDK inhibitors can be selected on the basis of inhibitory specificity for plant CDK's relative to the mammalian enzyme. For example, a plant CDK can be disposed in a differential screen with one or more of the human enzymes to select those compounds of greatest selectivity for inhibiting the plant enzyme. Thus, the present invention specifically contemplates formulations of the subject CDK inhibitors for agricultural applications, such as in the form of a defoliant or the like.

For agricultural and horticultural purposes the compounds of the invention may be used in the form of a composition formulated as appropriate to the particular use

and intended purpose. Thus the compounds may be applied in the form of dusting powders, or granules, seed dressings, aqueous solutions, dispersions or emulsions, dips, sprays, aerosols or smokes. Compositions may also be supplied in the form of dispersible powders, granules or grains, or concentrates for dilution prior to use.

- 5 Such compositions may contain such conventional carriers, diluents or adjuvants as are known and acceptable in agriculture and horticulture and they are manufactured in accordance with conventional procedures. The compositions may also incorporate other active ingredients, for example, compounds having herbicidal or insecticidal activity or a further fungicide. The compounds and
- 10 compositions can be applied in a number of ways, for example they can be applied directly to the plant foliage, stems, branches, seeds or roots or to the soil or other growing medium, and they may be used not only to eradicate disease, but also prophylactically to protect the plants or seeds from attack. By way of example, the compositions may contain from 0.01 to 1 wt.% of the active ingredient. For field
- 15 use, likely application rates of the active ingredient may be from 50 to 5000 g/hectare.

- The invention also contemplates the use of the compounds of the formula (I) in the control of wood decaying fungi and in the treatment of soil where plants grow, paddy fields for seedlings, or water for perfusion. Also contemplated by the
- 20 invention is the use of the compounds of the formula (I) to protect stored grain and other non-plant loci from fungal infestation.

EXAMPLES

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

- 25 In the examples, the compounds prepared were characterised by liquid chromatography and mass spectroscopy using two systems, the details of which are set out below. Where chlorine is present, the mass quoted for the compound is for ³⁵Cl. The two systems were equipped with identical chromatography columns and

were set up to run under the same operating conditions. The operating conditions used are also described below.

Platform system

- System: Waters 2790/Platform LC
- 5 Mass Spec Detector: Micromass Platform LC
- PDA Detector: Waters 996 PDA

Analytical conditions:

- Eluent A: 5% CH₃CN in 95% H₂O (0.1% Formic Acid)
- Eluent B: CH₃CN (0.1% Formic Acid)
- 10 Gradient: 10-95% eluent B
- Flow: 1.2 ml/min
- Column: Synergi 4µm Max-RP C₁₂, 80A, 50 x 4.6 mm (Phenomenex)

MS conditions:

- Capillary voltage: 3.5 kV
- 15 Cone voltage: 30 V
- Source Temperature: 120 °C

FractionLynx system

- System: Waters FractionLynx (dual analytical/prep)
- Mass Spec Detector: Waters-Micromass ZQ
- 20 PDA Detector: Waters 2996 PDA

Analytical conditions:

- Eluent A: 5% CH₃CN in 95% H₂O (0.1% Formic Acid)
- Eluent B: CH₃CN (0.1% Formic Acid)
- Gradient: 5-95% eluent B
- 25 Flow: 1.2 ml/min
- Column: Synergi 4µm Max-RP C₁₂, 80A, 50 x 4.6 mm (Phenomenex)

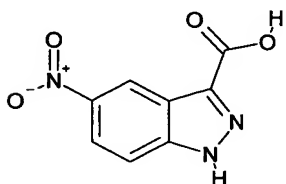
MS conditions:

Capillary voltage:	3.5 kV
Cone voltage:	30 V
Source Temperature:	120 °C
5 Desolvation Temperature:	300 °C

The starting materials for each of the Examples are commercially available unless otherwise specified.

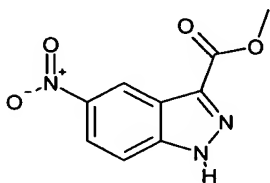
EXAMPLE 1

10 **Preparation of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide**

1A. Preparation of 5-Nitro-1H-indazole-3-carboxylic acid

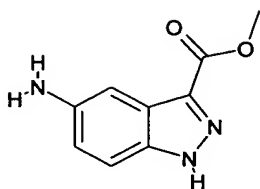
15 To a suspension of indazole-3-carboxylic acid (Fluka) (5 g, 31mmol) in concentrated H₂SO₄ (30 ml) at 0 °C was added KNO₃ (3.13 g, 31 mmol). The reaction was allowed to stir overnight at room temperature, then diluted with water and the products were extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over MgSO₄. Evaporation to dryness left the product as a yellow solid as a 7:3 mixture with the 7-nitro isomer; LCMS 2.58 min, *m/z* [M+H]⁺ 208.

20 **1B. Preparation of 5-Nitro-1H-indazole-3-carboxylic acid methyl ester**



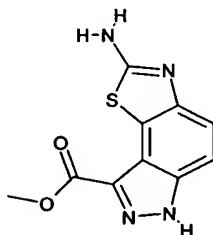
To a suspension of the carboxylic acid 1A (2.5 g, 12.1 mmol) in methanol (40 ml) was added concentrated hydrochloric acid (3 drops). The reaction was heated to reflux overnight. The reaction was allowed to cool to room temperature. The solid was filtered and dried in a vacuum oven to leave a yellow solid; LCMS 3.30 min, m/z $[M+H]^+$ 222 and m/z $[2M+H]^+$ 443.

1C. Preparation of 5-Amino-1H-indazole-3-carboxylic acid methyl ester



To a suspension of the nitro-indazole 1B (1.23 g, 5.57 mmol) in ethanol (10 ml) was added ethyl acetate (50 ml) and then Pd/C (56 mg) under a nitrogen atmosphere. The atmosphere was exchanged for H_2 , and H_2 was bubbled through the reaction mixture for 5 minutes. After three hours the compound was observed to have dissolved completely. The reaction mixture was filtered through Celite and the filtrate evaporated to dryness to leave the product amine [which contains approximately 25% of the 7-nitro isomer] as a yellow solid; LCMS 2.68 minutes, $[M+H]^+ = 192$.

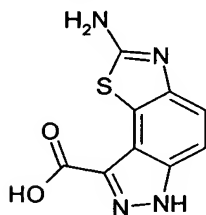
1D. Preparation of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid methyl ester



To a solution of the indazole 1C (50 mg, 0.26 mmol) in methanol (1 ml) and $-5\text{ }^{\circ}\text{C}$ was added and KSCN (28 mg, 0.29 mmol) and then bromine (7 μl , .13 mmol) slowly. The reaction was left at $-5\text{ }^{\circ}\text{C}$ for 2 hours. A brown suspension was observed to form. The reaction was allowed to warm to room temperature and was

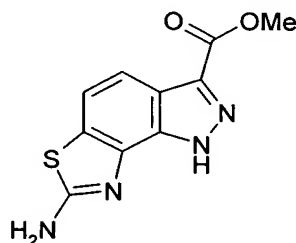
filtered. The solid was washed with methanol and dried in a vacuum oven to leave a grey solid; LCMS 1.85 min, m/z $[M+H]^+$ 249.

1E. Preparation of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-
carboxylic acid



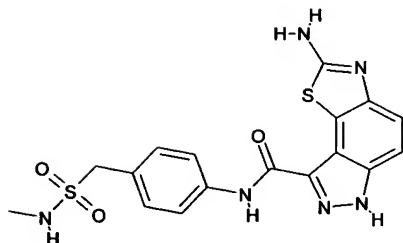
The methyl ester 1D (790 mg, 3.19 mmol) was suspended in tetrahydrofuran (THF): H₂O (24 ml, 3:1) and LiOH.H₂O (268 mg, 6.37 mmol) was added. The reaction was warmed to 50 °C and left to stir overnight. The reaction mixture was then neutralised, the solvent was evaporated and ethanol was added. The mixture was heated until boiling and the salts were filtered off. The filtrate was evaporated and the product was dried in a vacuum oven to leave the carboxylic acid as a red solid; LCMS 1.53 min, m/z $[M+H]^+$ 235.

1F. 7-Amino-1H-pyrazolo[3',4':3,4] benzo[1,2-d]thiazole-3-carboxylic acid methyl
ester



To the methanolic filtrate of Example 1D was added aqueous sodium thiosulphate and the resulting brown precipitate was filtered off to give 1.5 g of impure adduct, of which 50 mg was purified by preparative HPLC to yield approx 8 mg of the title compound.

1G. Preparation of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-
carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide



To the carboxylic acid 1E (12 mg, 0.05 mmol) in *N*-methyl pyrrolidine (NMP) (1.5 ml) was added EDC (16 mg, 0.10 mmol), HOBT (14 mg, 0.10 mmol), NMM (11 μ l, 0.10 mmol) and then (4-aminophenyl)-*N*-methanesulfonamide (15 mg, 0.8 mmol) at room temperature. The reaction was heated to 80 °C for 2 hours and then cooled. Ethyl acetate and Na₂CO₃ (aq., sat.) were added (30 ml, 1:1) and the organic layer was separated. The aqueous layer was washed again with ethyl acetate and the combined organic layers were washed with water, then brine and dried over MgSO₄. The product was filtered and evaporated to dryness.

Purification by preparative HPLC gave the product as a yellow solid; LCMS 2.21 min, m/z [M+H]⁺ 417.

EXAMPLE 2

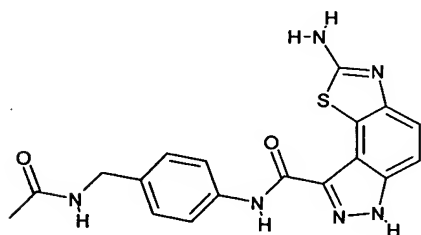
General Amide Preparative Procedure A

To the carboxylic acid 1E (12 mg, 0.05 mmol) in *N*-methyl pyrrolidine (NMP) (1.5 ml) was added EDC (16 mg, 0.10 mmol), HOBT (or HOAt) (0.10 mmol), NMM (11 μ l, 0.10 mmol) and the corresponding amine or appropriately substituted aniline (0.08 mmol, 1.6 equiv.) at room temperature. The reaction mixture was heated to 80 °C for 2 hours and then cooled. Ethyl acetate and Na₂CO₃ (aq.) were added (30 ml, 1:1) and the organic layer was separated. The aqueous layer was washed again with ethyl acetate and the combined organic layers were washed with water, then brine and dried over MgSO₄. The product was filtered and evaporated to dryness. The compounds were purified by flash column chromatography, and characterised by liquid chromatography and mass spectrometry using either of the systems described above.

EXAMPLE 3General Amide Preparative Procedure B

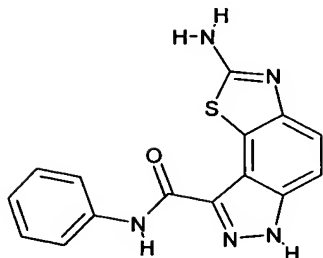
To a solution of carboxylic acid 1E (0.59 g, 2.5 mmol) in *N*-methyl pyrrolidine (NMP) (10 ml) was added the corresponding amine (1.2 equiv), *N,N*-diisopropylethylamine (1.6 ml, 9.0 mmol, 3.6 equiv.) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (1.05 g, 2.75 mmol, 1.1 equiv.). The mixture was stirred for a period of 24-72 hours and additional *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate was added if necessary. The reaction was quenched with water (10 ml) and dichloromethane (10 ml). The compounds were purified by filtering off the precipitated product and then triturating the resulting solid with water and dichloromethane. The product was characterised by liquid chromatography and mass spectrometry using either of the systems described above.

Using either preparative method A or preparative method B, the following compounds were prepared.

EXAMPLE 4Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid [4-(acetylamino-methyl)-phenyl]-amide

Procedure A was followed using HOBt. LCMS 2.05 min, m/z $[M+H]^+$ 381.

EXAMPLE 5Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid phenylamide

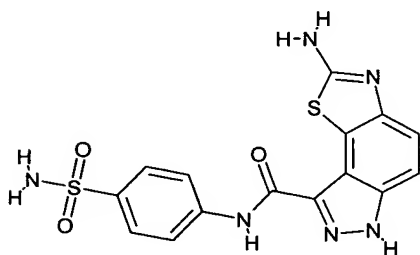


Procedure A was followed using HOBt. LCMS 2.23 min, m/z $[M+H]^+$ 310.

EXAMPLE 6

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-sulfamoyl-phenyl)-amide

5

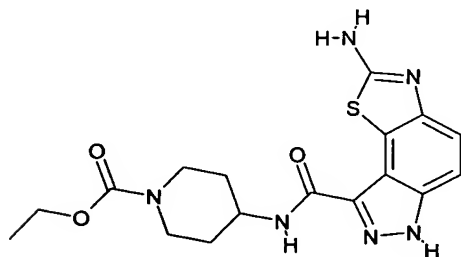


Procedure A was followed using HOBt. LCMS 1.86 min, m/z $[M+H]^+$ 389.

EXAMPLE 7

Synthesis of 4-[(2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carbonyl)-amino]-piperidine-1-carboxylic acid ethyl ester

10

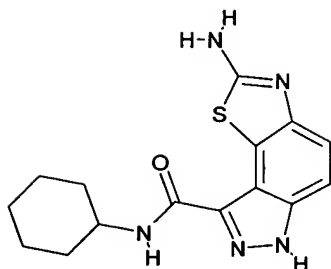


Procedure B was followed. LCMS 2.08 min, m/z $[M+H]^+$ 389.

EXAMPLE 8

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid cyclohexylamide

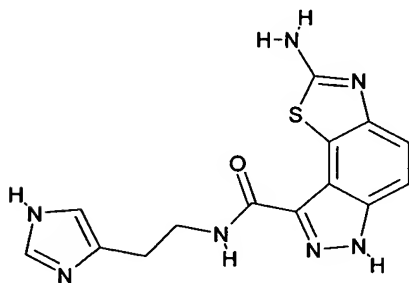
15



Procedure B was followed. LCMS 2.3 min, m/z $[M+H]^+$ 316.

EXAMPLE 9

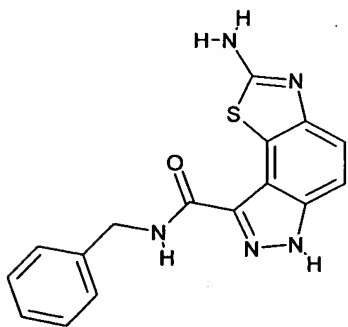
5 Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid [2-(1H-imidazol-4-yl)-ethyl]-amide



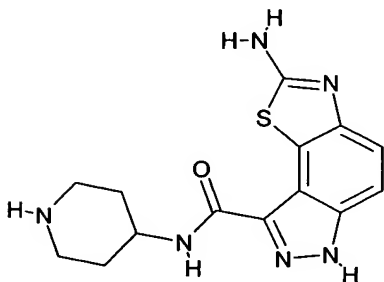
Procedure A was followed using HOBT. LCMS 0.49 min, m/z $[M+H]^+$ 328.

EXAMPLE 10

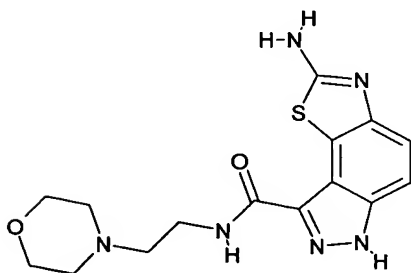
10 Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid benzylamide



Procedure A was followed using HOAt. LCMS 2.23 min, m/z $[M+H]^+$ 324.

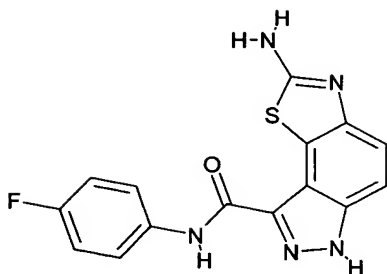
EXAMPLE 11Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid piperidin-4-ylamide

- 5 4-Amino-1-BOC-piperidine was coupled to carboxylic acid 1E with a standard EDC / HOBT coupling as outlined above in Procedure A. The BOC compound) (20 mg, 0.06 mmol) was then treated with HCl saturated EtOAc (5ml), and stirred at room temperature overnight. The precipitated solid was filtered off and purified by preparative HPLC that gave product as an off white solid; LCMS 0.4 min, m/z [M+H]⁺ 317.
- 10

EXAMPLE 12Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

- 15 Procedure A was followed using HOAt. LCMS 0.44 min, m/z [M+H]⁺ 346.

EXAMPLE 13Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide

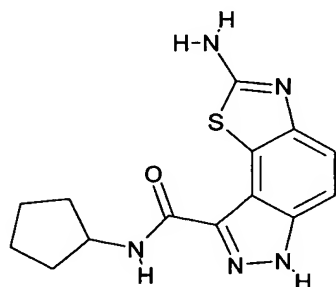


Procedure A was followed using HOAt. LCMS 2.32 min, m/z $[M+H]^+$ 327.

EXAMPLE 14

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid cyclopentylamide

5

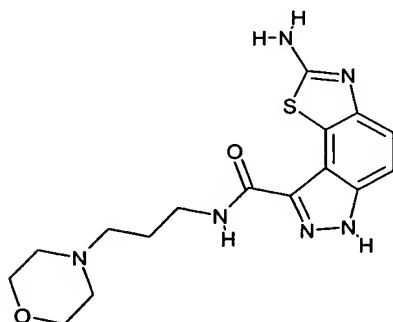


Procedure A was followed using HOAt. LCMS 2.09 min, m/z $[M+H]^+$ 301.

EXAMPLE 15

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (3-morpholin-4-yl-propyl)-amide

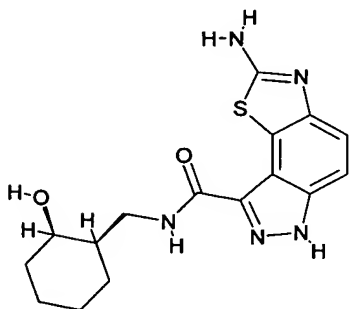
10



Procedure A was followed using HOAt. LCMS 0.52 min, m/z $[M+H]^+$ 361.

EXAMPLE 16

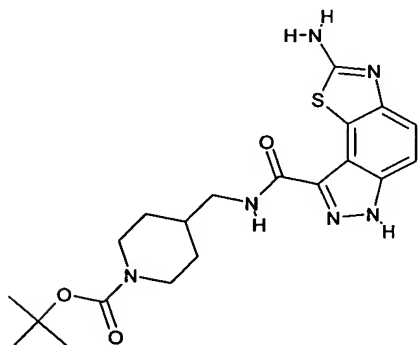
Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (2-hydroxy-cyclohexylmethyl)-amide



- 5 Procedure A was followed using HOAt. LCMS 1.81 min, m/z $[M+H]^+$ 346.

EXAMPLE 17

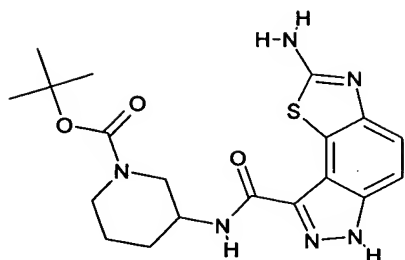
Synthesis of 4-{[(2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carbonyl)-amino]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester



- 10 Procedure A was followed using HOAt. LCMS 2.46 min, m/z $[M+H]^+$ 431.

EXAMPLE 18

Synthesis of 3-[(2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carbonyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester

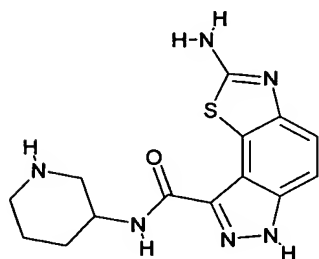


Procedure A was followed using HOAt. LCMS 2.46 min, m/z $[M+H]^+$ 417.

EXAMPLE 19

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid piperidin-3-ylamide

5

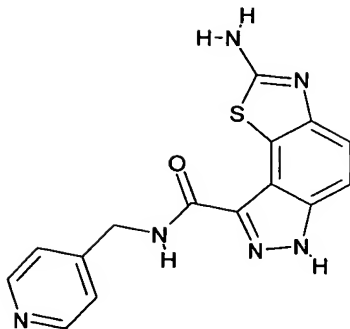


To a suspension of Compound 18 above (0.1g, 0.24mmol) in CH_2Cl_2 (2ml) was added TFA (0.2ml), and the reaction was stirred room temperature for 1 hour. The precipitated solid was filtered and washed with CH_2Cl_2 followed by ether. The product was dried in vacuum oven to give an off white solid; LCMS 0.62 min, m/z $[M+H]^+$ 317.

10

EXAMPLE 20

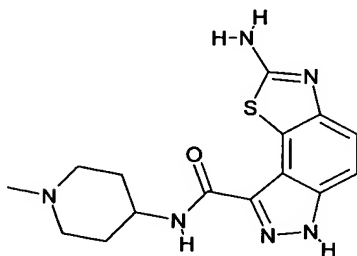
Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (pyridin-4-ylmethyl)-amide



Procedure A was followed using HOAt. LCMS 0.61 min, m/z $[M+H]^+$ 324.

EXAMPLE 21

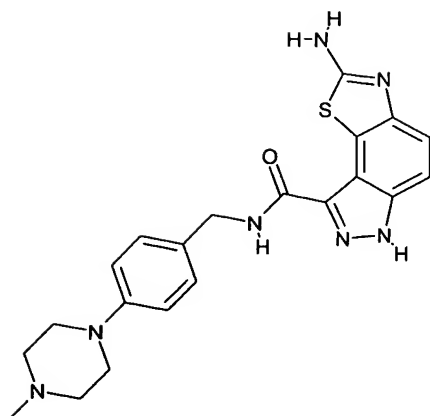
Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (1-methyl-piperidin-4-yl)-amide



Procedure A was followed using HOAt. LCMS 0.49 min, m/z $[M+H]^+$ 331.

EXAMPLE 22

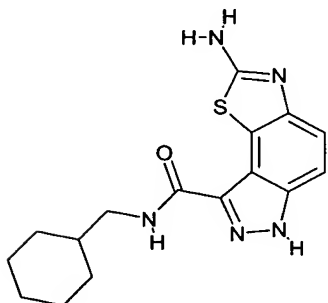
Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid 4-(4-methyl-piperazin-1-yl)-benzylamide



Procedure A was followed using HOAt. LCMS 0.70 min, m/z $[M+H]^+$ 422.

EXAMPLE 23

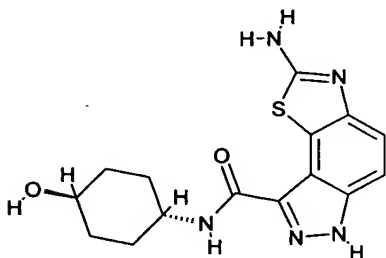
Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic
5 acid cyclohexylmethyl-amide



Procedure A was followed using HOAt. LCMS 2.51 min, m/z $[M+H]^+$ 330.

EXAMPLE 24

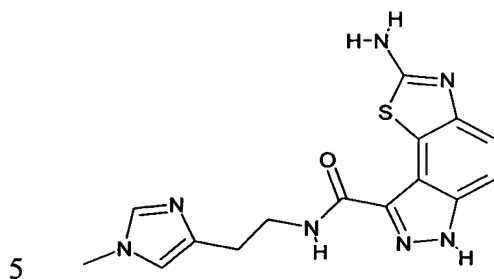
Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic
10 acid (4-hydroxy-cyclohexyl)-amide



Procedure A was followed using HOAt. LCMS 0.71 min, m/z $[M+H]^+$ 331.

EXAMPLE 25

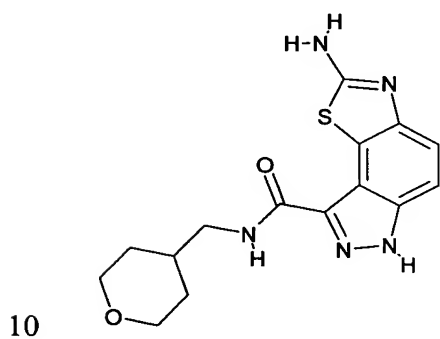
Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid [2-(1-methyl-1H-imidazol-4-yl)-ethyl]-amide



Procedure A was followed using HOAt. LCMS 0.61 min, m/z $[M+H]^+$ 342.

EXAMPLE 26

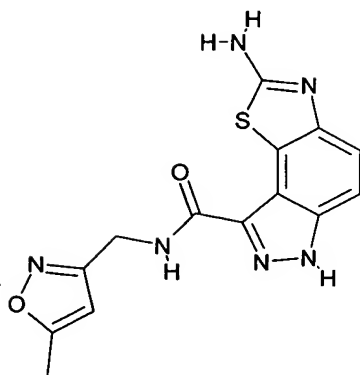
Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



Procedure A was followed using HOAt. LCMS 1.71 min, m/z $[M+H]^+$ 332.

EXAMPLE 27

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (5-methyl-isoxazol-3-ylmethyl)-amide

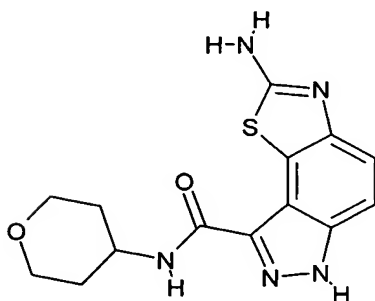


Procedure A was followed using HOAt. LCMS 1.80 min, m/z $[M+H]^+$ 329.

EXAMPLE 28

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (tetrahydro-pyran-4-yl)-amide

5

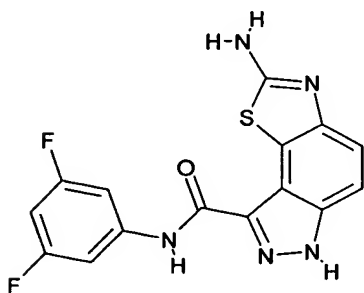


Procedure A was followed using HOAt. LCMS 0.67 min, m/z $[M+H]^+$ 318.

EXAMPLE 29

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (3,5-difluoro-phenyl)-amide

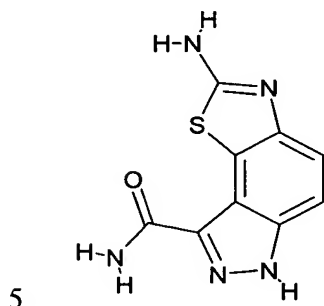
10



Procedure A was followed using HOAt. LCMS 2.63 min, m/z $[M+H]^+$ 346.

EXAMPLE 30

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid amide



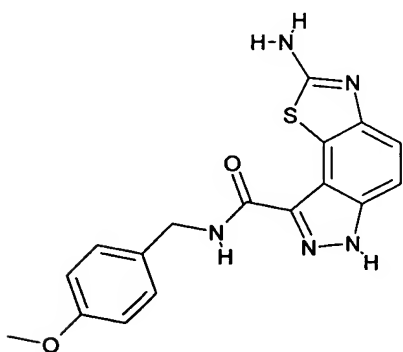
Compound 1E (0.1 g, 0.43mmol) was suspended in NMP (1 ml) and treated with 2-(1-oxy-pyridin-2-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate [TOTT] (0.2g, 0.64mmol) followed by DIPEA (0.14ml, 0.85mmol) and ammonium chloride (0.046g, 0.85mmol). Reaction was stirred at room temperature for 2 hours and then diluted with CH_2Cl_2 to precipitate a solid, which was purified by preparative HPLC affording the product as a off white solid; LCMS 2.71 min, m/z $[M+H]^+$ 234.

10

EXAMPLE 31

Synthesis of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid 4-methoxy-benzylamide

15

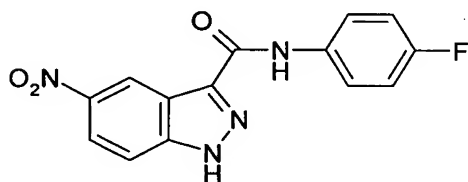


Procedure A was followed using HOAt. LCMS 2.15 min, m/z $[M+H]^+$ 354.

EXAMPLE 32

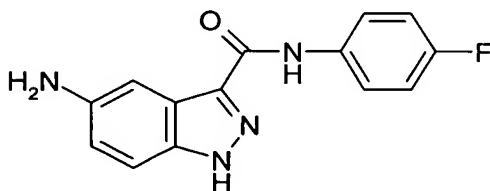
Synthesis of 2-ethylamino-6H-pyrazolo[4', 3':3, 4]benzo[1, 2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide

5 32A. Preparation of 5-nitro-1H-indazole-3-carboxylic acid (4-fluorophenyl)-amide



To a solution of 5-nitro-1H-indazole-3-carboxylic acid, 1A (6.5g, 31.5 mmol, 1.0 equiv) in DMF (200 ml) was added 4-fluoroaniline (33.3 ml 34.6 mmol, 1.1 equiv), HOBT (5.1g, 37.7 mmol, 1.2 equiv) and EDC (7.2 g, 37.7 mmol, 1.2 equiv). The mixture was stirred for a period of 72 hours. The solvent was removed under reduced pressure and the resulting solid suspended in ethyl acetate and aqueous sodium hydrogen carbonate. The precipitate was collected, resuspended in aqueous sodium hydrogen carbonate and stirred for 10 mins. The solid was collected and dried in a vacuum oven to afford the title compound (7.77 g, 82%) as a 8:2 mixture with the 7-nitro isomer; LCMS 3.83 min, m/z $[M+H]^+$ 300.

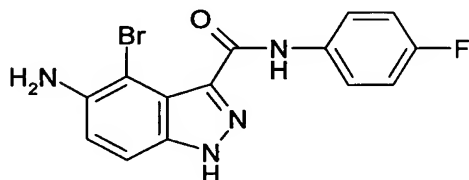
32B. Preparation of 5-amino-1H-indazole-3-carboxylic acid (4-fluorophenyl)-amide



A mixture of compound 32A (7.3 g, 24.3 mmol), 10% Pd/C (0.7 g), ethanol (200 ml) and DMF (200ml) under an atmosphere of nitrogen was stirred under an atmosphere of hydrogen for 18hr. The catalyst was then removed and the filtrate

was evaporated to dryness, to give the title compound (4.94 g, 75%) as a 8:2 mixture with the 7-nitro isomer; LCMS 1.95 min, m/z $[M+H]^+$ 270.

32C. Preparation of 5-Amino-4-bromo-1H-indazole-3-carboxylic acid (4-fluorophenyl)-amide

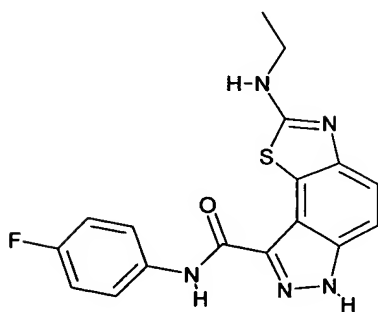


5

Bromine was added dropwise to a stirred suspension of 32B (4.9 g, 18.3 mmol) in MeOH (10.5 ml) at -5°C. The reaction mixture was stirred at -5°C for 1 hour, and then allowed to warm to 10°C. The reaction was poured into aqueous sodium thiosulphate solution and the suspension was stirred. The solid was collected, washed with water and then dried in a vacuum oven to afford the title compound 32C (6.9 g) that was used without further purification; LCMS 2.89 min, m/z $[M+H]^+$ 348.

10

32D. Preparation of 2-ethylamino-6H-pyrazolo[4', 3':3, 4]benzo[1, 2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide



15

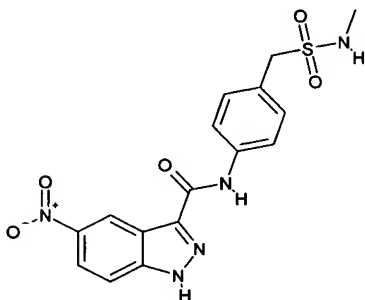
Ethyl isothiocyanate (27.5 mg, 0.315 mmol) was added to a solution of compound 32C (100 mg, 0.287 mmol) in methanol (5 ml) and the reaction mixture was heated in the microwave at 150°C (50W) for 10 minutes. The solvent was removed by evaporation, the crude product was purified by preparative LCMS and after

evaporation of product-containing fractions gave 13 mg (12.8%) of product;
LCMS 2.65 min, m/z $[M+H]^+$ 356.

EXAMPLE 33

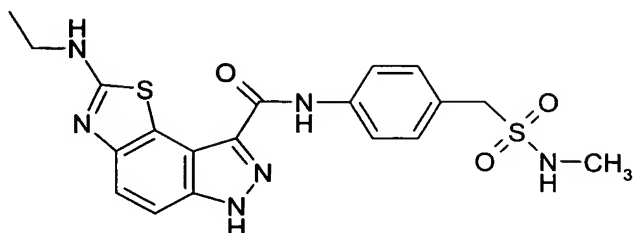
Synthesis of 2-Ethylamino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-
5 carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide

33A. Preparation of 5-Nitro-1H-indazole-3-carboxylic acid (4-
methylsulfamoylmethyl-phenyl)-amide



To compound 1A in dichloromethane (8 ml) and was added (4-amino-phenyl)-N-
10 methyl-methane sulfonamide (1.2 equiv), *N,N*-diisopropylethylamine (1.2 ml, 7.2
mmol, 3.6 equiv) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium
hexafluorophosphate (0.84 g, 2.20 mmol, 1.1 equiv). The mixture was stirred for a
period of 24-72 hours and was then quenched with water (8 ml) and
dichloromethane (8 ml). Water and dichloromethane were removed by filtration
15 and the solid was triturated with water and dichloromethane. The title compound
was further purified by preparative; LCMS 3.30 min, m/z $[M+H]^+$ 390.

33B. Preparation of 2-Ethylamino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-
carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide

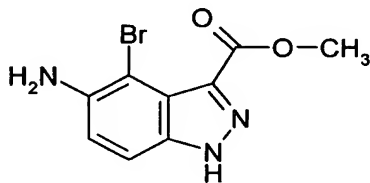


To a suspension of the indazole 33A (150 mg, 0.39 mmol) in ethanol:DMF (1:1, 2 ml) was added Pd/C (40 mg) under a nitrogen atmosphere. The atmosphere was exchanged for H₂, and H₂ was bubbled through the reaction mixture for 5 minutes. After 16 hours the reaction mixture was filtered through Celite and the filtrate evaporated to dryness to leave the product. To a suspension of the resultant amine (200 mg, 0.56 mmol) in MeOH (3.5 ml) at -5 °C was slowly added ethyl isothiocyanate (55 ul, 0.61 mmol) and bromine (14 ul, 0.28 mmol). The reaction was stirred at -5 °C for 1 hour and allowed to warm to room temperature for 16 hours. The reaction was poured into sodium thiosulphate (aq., sat.) and the product extracted with EtOAc. The combined organic layers were washed with water, brine and then dried over MgSO₄. The product was filtered and evaporated under reduced pressure to yield the bromide as a red solid. The bromide (50 mg, 0.11 mmol) was taken up in MeOH (0.7 ml) and the ethyl isothiocyanate (0.113 ul, 1.25 mmol) added. The reaction was heated to 70 °C for 16 hours. Purification by HPLC yielded a peach colored solid; LCMS 2.20 min, *m/z* [M+H]⁺ 445.

EXAMPLE 34

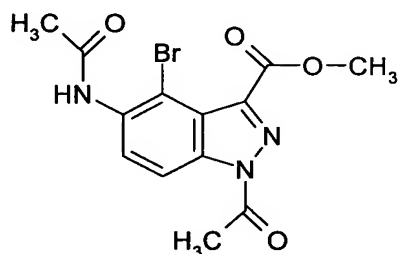
Synthesis of 2-Methyl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide

34A. Preparation of 5-Amino-4-bromo-1H-indazole-3-carboxylic acid, methyl ester



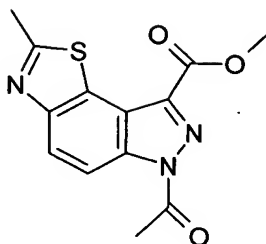
To a solution of the amine 1C (50 mg, 0.26 mmol) in THF (1 ml) at -5°C was added 1 drop of conc H_2SO_4 and NBS (46 mg, 0.26 mmol) slowly. The reaction was kept at -5°C for 90 minutes. Approximately 100 mg of Na_2CO_3 was added followed by sodium thiosulphate (aq., sat.). The reaction was allowed to warm to room temperature and the product was extracted with EtOAc (x2). The combined organic layers were washed with water, brine and the dried over MgSO_4 . The product was filtered and evaporated under reduced pressure. The product was purified by flash chromatography to yield the bromide 34A as colourless crystals; LCMS 2.41 min, m/z $[\text{M}+\text{H}]^+$ 270/272.

10 34B. Preparation of 1-Acetyl-5-acetylamino-4-bromo-1H-indazole-3-carboxylic acid methyl ester



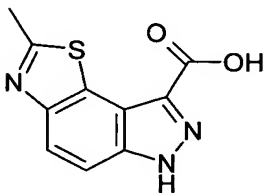
To a suspension of the indazole 34A (2.0 g, 7.4 mmol) in DCM (25 ml) at -78°C was added Et_3N (1.23 ml, 8.9 mmol), and then the acetyl chloride (0.7 ml, 8.1 mmol) was added dropwise. The reaction was allowed to stir for 1 hour at -78°C and then warmed to room temperature. The reaction was quenched with Na_2CO_3 (aq., sat.) and extracted with EtOAc (x3). The combined organic layers were washed with water and brine then dried over MgSO_4 . The product was filtered and evaporated under reduced pressure to yield a brown solid. The compound was dried in a vacuum oven, and purified by flash column chromatography (gradient elution with DCM:EtOAc) to yield the two products as yellow solids; LCMS 2.92 min, m/z $[\text{M}+\text{H}]^+$ 312/314; LCMS 3.34 min, m/z $[\text{M}+\text{H}]^+$ 353/355.

20 34C. Preparation of 6-Acetyl-2-methyl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid methyl ester



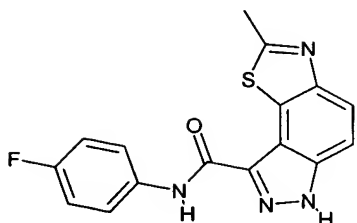
To a suspension of the indazole 34B (100 mg, 0.28 mmol) in toluene (2.0 ml) was added the Lawesson's reagent (59 mg, 0.14), under N₂. The mixture was heated to reflux for 1 hour. The reaction was allowed to cool and was filtered through a silica column with gradient elution EtOAc:DCM. The filtrate was evaporated to dryness under reduced pressure. On addition of methanol the product 34C precipitated and was filtered, and was taken on to the next reaction crude; LCMS 3.91 min, *m/z* [M+H]⁺ 290.

10 34D. Preparation of 2-methyl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid



The methyl ester 34C (24 mg, 0.08 mmol) was suspended in tetrahydrofuran (THF): H₂O (3 ml, 3:1) and LiOH.H₂O (7μg, 0.17 mmol) was added. The reaction mixture was warmed to 50 °C and left to stir overnight. The solvent was evaporated and ethanol added. The mixture was heated until boiling then filtered. The solid was dried in a vacuum oven to leave the title carboxylic acid; LCMS 2.06 min, *m/z* [M+H]⁺ 234.

34E. Synthesis of 2-Methyl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide

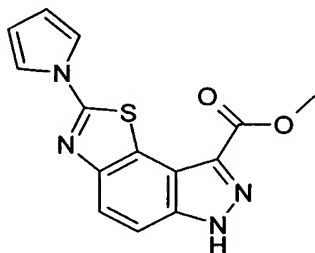


Procedure A was followed using HOAt using compound 34D and 4-fluoroaniline; LCMS 3.62 min, m/z $[M+H]^+$ 327.

EXAMPLE 35

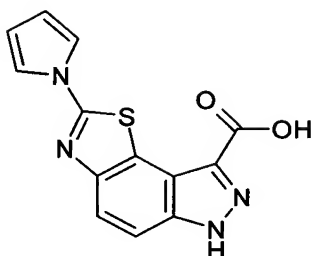
5 Synthesis of 2-Pyrrol-1-yl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide

35A. Preparation of 2-Pyrrol-1-yl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid methyl ester



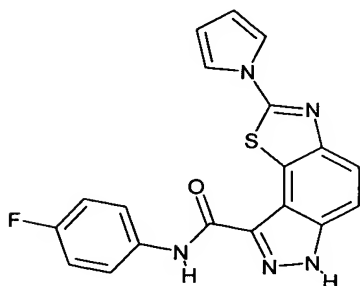
- 10 To a mixture of the indazole 1D (100 mg, 0.40 mmol) in acetic acid (1.3 ml) was added sodium acetate (0.66 mg, 0.48 mmol) and 2,5-dimethoxytetrahydrofuran (0.117 ml, 0.89 mmol). The reaction was heated to 120 °C for 3.5 hours. The reaction was cooled and quenched with water (10 ml). The precipitate was filtered and was dried under reduced pressure and evaporated from toluene twice to leave a
- 15 solid 35A, which was taken on to the next reaction; LCMS 3.64 min, m/z $[M+H]^+$ 299.

35B. Preparation of 2-Pyrrol-1-yl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid



The methyl ester 35A was subjected to lithium hydroxide hydrolysis as described above. The solid was dried in a vacuum oven to leave the carboxylic acid 35B; LCMS 3.05 min, m/z $[M+H]^+$ 285.

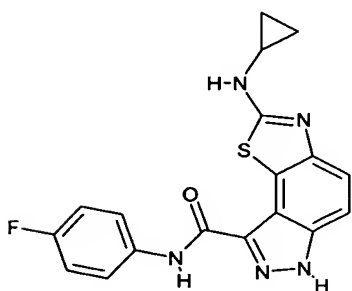
5 35C. Preparation of 2-Pyrrol-1-yl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide



Procedure A was followed using HOAt using 35B and 4-fluoroaniline; LCMS 4.55 min, m/z $[M+H]^+$ 378.

10 EXAMPLE 36

Synthesis of 2-cyclopropylamino-6H-pyrazolo[4', 3': 3, 4]benzo[1, 2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide

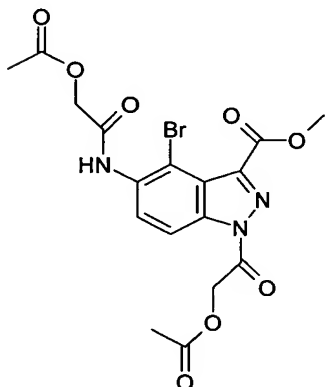


Cyclopropyl isothiocyanate (59 μ l, 0.63 mmol) was added to a solution of 5-amino-4-bromo-1H-indazole-3-carboxylic acid (4-fluoro-phenyl)-amide (Compound 32C) (200 mg, 0.57 mmol) in methanol (5 ml) and the reaction mixture was heated in the microwave at 120°C (50W) for 15 minutes. The solvent was removed by evaporation, the crude product was purified by preparative LC/MS and after evaporation of product-containing fractions gave 10 mg (4.8%) of product as a brown solid; LC/MS 2.90 min, m/z $[M+H]^+$ 367.66.

EXAMPLE 37

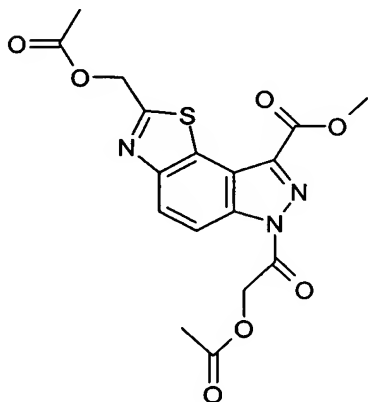
Synthesis of 2-Hydroxymethyl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide

37A. Preparation of 1-(2-acetoxy-acetyl)-5-(2-acetoxy-acetyl-amino)-4-bromo-1H-indazole-3-carboxylic acid methyl ester



To a suspension of the indazole 34A (780 mg, 2.89 mmol) in DCM (9.6 ml) at -78 °C was added Et₃N (922 μ l, 6.64 mmol), and then the acetoxyacetyl chloride (704 μ l, 6.35 mmol) was added dropwise. The reaction was allowed to stir for 2 hours at -78 °C and the warm to room temperature over another 2 hours. The reaction was quenched with Na₂CO₃ (aq., sat.) and extracted with EtOAc (x3). The combined organic layers were washed with water and brine then dried over MgSO₄. The product was filtered and evaporated under reduced pressure to yield a brown solid. The compound 37A was dried in a vacuum oven, and taken onto the next reaction; LCMS 3.26 min, m/z $[M+H]^+$ 470/472.

37B. Preparation of 6-(2-acetoxy-acetyl)-2-(2-acetoxy-methyl)-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid methyl ester



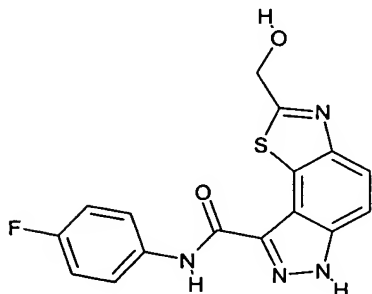
To a suspension of the indazole 37A (320 mg, 0.68 mmol) in toluene (4.5 ml) was added the Lawesson's reagent (165 mg, 0.41), under N₂. The mixture was heated to reflux for 16 hours. The reaction was allowed to cool and was filtered through a silica column eluting with 1:1 EtOAc:MeOH. The filtrate was evaporated to dryness under reduced pressure. On addition of MeOH the product precipitated, was filtered and dried in a vacuum oven. The product 37B was taken on to the next reaction crude; LCMS 3.59 min, m/z [M+H]⁺ 406.

37C. Preparation of 2-Hydroxymethyl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid



The methyl ester 37B was subjected to lithium hydroxide hydrolysis as described above. The solid was dried in a vacuum oven to leave the carboxylic acid 37C; LCMS 1.70 min, m/z [M+H]⁺ 249.

37D. Synthesis of 2-Hydroxymethyl-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-fluoro-phenyl)-amide



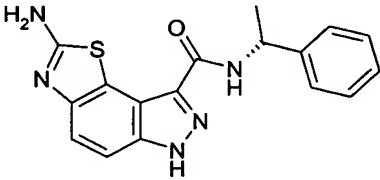
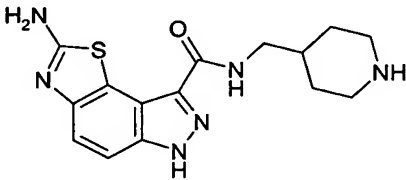
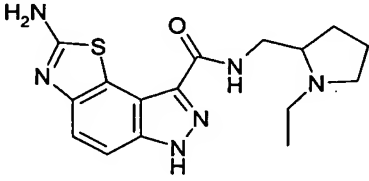
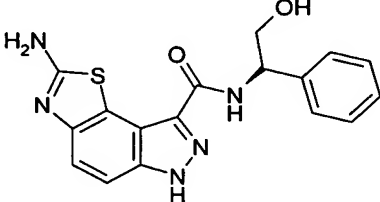
Procedure A was followed using HOBT using 37C and 4-fluoroaniline; LCMS
 5 2.92 min, m/z $[M+H]^+$ 343.

EXAMPLES 38 – 43

Using the synthetic methods described above and the appropriate starting materials, the compounds set out in Table 2 below were prepared.

Table 2

Example	Compound
38	
39	

40	
41	
42	
43	

BIOLOGICAL ACTIVITY

EXAMPLE 44

Measurement of CDK2 Kinase Inhibitory Activity (IC₅₀)

- 5 Compounds of the invention were tested for kinase inhibitory activity using the following protocol.

1.7 μ l of active CDK2/CyclinA (Upstate Biotechnology, 10U/ μ l) is diluted in assay buffer (250 μ l of 10X strength assay buffer (200mM MOPS pH 7.2, 250mM β -

glycerophosphate, 50mM EDTA, 150mM MgCl₂), 11.27 µl 10mM ATP, 2.5 µl 1M DTT, 25 µl 100mM sodium orthovanadate, 708.53 µl H₂O), and 10 µl mixed with 10 µl of histone substrate mix (60 µl bovine histone H1 (Upstate Biotechnology, 5 mg/ml), 940 µl H₂O, 35 µCi γ³³P-ATP) and added to 96 well plates along with 5 µl of various dilutions of the test compound in DMSO (up to 2.5%). The reaction is allowed to proceed for 5 hours before being stopped with an excess of ortho-phosphoric acid (30 µl at 2%).

γ³³P-ATP which remains unincorporated into the histone H1 is separated from phosphorylated histone H1 on a Millipore MAPH filter plate. The wells of the MAPH plate are wetted with 0.5% orthophosphoric acid, and then the results of the reaction are filtered with a Millipore vacuum filtration unit through the wells. Following filtration, the residue is washed twice with 200 µl of 0.5% orthophosphoric acid. Once the filters have dried, 25 µl of Microscint 20 scintillant is added, and then counted on a Packard Topcount for 30 seconds.

The % inhibition of the CDK2 activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the CDK2 activity (IC₅₀).

The compounds of Examples 1D, 1F, 1G and 4 to 43 all had IC₅₀ values of less than 20 micromoles, or exhibit at least 50% inhibition at a concentration of 0.03 micromoles, and the great majority had IC₅₀ values of less than 1 micromole.

PHARMACEUTICAL FORMULATIONS

EXAMPLE 45

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50mg of the compound with 197mg of lactose (BP) as diluent, and 3mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

5 EXAMPLE 46

Determination of Antifungal Activity

The antifungal activity of the compounds of the formula (I) is determined using the following protocol.

10 The compounds are tested against a panel of fungi including *Candida parapsilosis*, *Candida tropicalis*, *Candida albicans*-ATCC 36082 and *Cryptococcus neoformans*. The test organisms are maintained on Sabourahd Dextrose Agar slants at 4 °C. Singlet suspensions of each organism are prepared by growing the yeast overnight at 27 °C on a rotating drum in yeast-nitrogen base broth (YNB) with amino acids (Difco, Detroit, Mich.), pH 7.0 with 0.05 morpholine propanesulphonic acid (MOPS). The suspension is then centrifuged and washed twice with 0.85% NaCl
15 before sonicating the washed cell suspension for 4 seconds (Branson Sonifier, model 350, Danbury, Conn.). The singlet blastospores are counted in a haemocytometer and adjusted to the desired concentration in 0.85% NaCl.

20 The activity of the test compounds is determined using a modification of a broth microdilution technique. Test compounds are diluted in DMSO to a 1.0 mg/ml ratio then diluted to 64 µg/ml in YNB broth, pH 7.0 with MOPS (Fluconazole is used as the control) to provide a working solution of each compound. Using a 96-well plate, wells 1 and 3 through 12 are prepared with YNB broth, ten fold dilutions of the compound solution are made in wells 2 to 11 (concentration ranges
25 are 64 to 0.125 µg/ml). Well 1 serves as a sterility control and blank for the spectrophotometric assays. Well 12 serves as a growth control. The microtitre plates are inoculated with 10 µl in each of well 2 to 11 (final inoculum size is 10⁴ organisms/ml). Inoculated plates are incubated for 48 hours at 35 °C. The MIC

values are determined spectrophotometrically by measuring the absorbance at 420 nm (Automatic Microplate Reader, DuPont Instruments, Wilmington, Del.) after agitation of the plates for 2 minutes with a vortex-mixer (Vorte-Genie 2 Mixer, Scientific Industries, Inc., Bolemia, N.Y.). The MIC endpoint is defined as the lowest drug concentration exhibiting approximately 50% (or more) reduction of the growth compared with the control well. With the turbidity assay this is defined as the lowest drug concentration at which turbidity in the well is <50% of the control (IC50). Minimal Cytolytic Concentrations (MCC) are determined by sub-culturing all wells from the 96-well plate onto a Sabourahd Dextrose Agar (SDA) plate, incubating for 1 to 2 days at 35 °C and then checking viability.

EXAMPLE 47

Protocol for the Biological Evaluation of Control of in vivo Whole Plant Fungal Infection

Compounds of the formula (I) are dissolved in acetone, with subsequent serial dilutions in acetone to obtain a range of desired concentrations. Final treatment volumes are obtained by adding 9 volumes of 0.05% aqueous Tween-20™ or 0.01% Triton X-100™, depending upon the pathogen.

The compositions are then used to test the activity of the compounds of the invention against tomato blight (*Phytophthora infestans*) using the following protocol. Tomatoes (cultivar Rutgers) are grown from seed in a soil-less peat-based potting mixture until the seedlings are 10-20 cm tall. The plants are then sprayed to run-off with the test compound at a rate of 100 ppm. After 24 hours the test plants are inoculated by spraying with an aqueous sporangia suspension of *Phytophthora infestans*, and kept in a dew chamber overnight. The plants are then transferred to the greenhouse until disease develops on the untreated control plants.

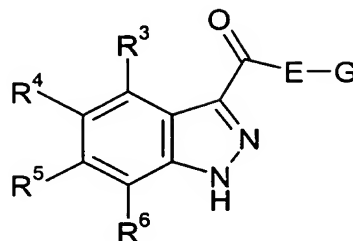
Similar protocols are also used to test the activity of the compounds of the invention in combatting Brown Rust of Wheat (*Puccinia*), Powdery Mildew of Wheat (*Erysiphe graminis*), Wheat (cultivar Monon), Leaf Blotch of Wheat (*Septoria tritici*), and Glume Blotch of Wheat (*Leptosphaeria nodorum*).

Equivalents

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations
5 may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. A compound of the formula (I):



(I)

5 wherein

E is O, S or NH;

G is selected from hydrogen; carbocyclic and heterocyclic groups having from 3 to 12 ring members; and acyclic C₁₋₈ hydrocarbyl groups optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the acyclic C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹; provided that E-G is not OH or SH and further provided that E-G does not contain the group O-O;

two adjacent moieties selected from R³, R⁴, R⁵ and R⁶, together with the carbon atoms to which they are attached, form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S; and the other two moieties selected from R³, R⁴, R⁵ and R⁶ are the same or different and are each selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, X¹C(X²), C(X²)X¹, X¹C(X²)X¹, S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents

- selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c,
 5 X¹C(X²), C(X²)X¹ or X¹C(X²)X¹;
 R^c is hydrogen or C₁₋₄ hydrocarbyl; and
 X¹ is O, S or NR^c and X² is =O, =S or =NR^c.
2. A compound according to claim 1 wherein R³ and R⁴, together with the carbon atoms to which they are attached, form a fused heterocyclic group.
- 10 3. A compound according to claim 1 or claim 2 wherein the fused heterocyclic ring is substituted by one or more groups R¹⁰ selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, X¹C(X²), C(X²)X¹, X¹C(X²)X¹,
 15 S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members, and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to
 20 12 ring members and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹;
 R^c is selected from hydrogen and C₁₋₄ hydrocarbyl; and
 X¹ is O, S or NR^c and X² is =O, =S or =NR^c.
- 25 4. A compound according to claim 3 wherein R¹⁰ is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic carbocyclic and heterocyclic groups having from 3 to 7 ring members, a group R^a-R^b wherein R^a is a bond, O, CO, X¹C(X²), C(X²)X¹, X¹C(X²)X¹,
 30 S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from hydrogen and a C₁₋₈ hydrocarbyl group optionally substituted by one or more

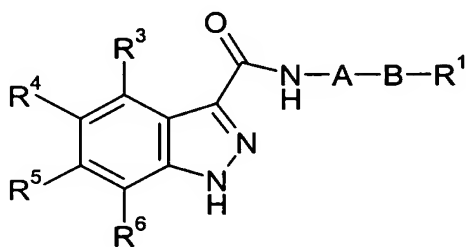
- substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹; and R^c, X¹ and X² are as
5 hereinbefore defined.
5. A compound according to claim 4 wherein the substituents R¹⁰ on the fused heterocyclic ring are selected from amino, mono or di-C₁₋₄ hydrocarbylamino, C₁₋₄ hydrocarbyl optionally substituted by hydroxyl or amino, and N-linked monocyclic heterocyclic groups containing 1, 2 or 3
10 heteroatoms selected from N, O and S.
6. A compound according to claim 5 wherein the substituents R¹⁰ are selected from amino, methylamino, ethylamino, cyclopropylamino, methyl, ethyl, hydroxymethyl, hydroxyethyl, N-pyrrolidinyl and N-imidazolyl.
7. A compound according to any one of the preceding claims wherein the
15 other two groups R³ to R⁶ not forming part of the fused heterocyclic ring are selected from hydrogen, halogen, hydroxy, cyano, methyl, ethyl, cyclopropyl, trifluoromethyl, or amino.
8. A compound according to claim 7 wherein the said groups are selected from hydrogen, methyl, fluorine or chlorine.
- 20 9. A compound according to claim 8 wherein the said groups are each hydrogen.
10. A compound according to any one of the preceding claims wherein the fused heterocyclic group is aromatic.
11. A compound according to any one of the preceding claims wherein the
25 fused heterocyclic group is a five or six membered ring, preferably a five membered ring.

12. A compound according to claim 11 wherein the fused ring is selected from thiazolo, isothiazolo, oxazolo, isoxazolo, pyrrolo, pyrido, thieno, furano, pyrimido, pyrazolo, pyrazino, and imidazolo fused rings.
13. A compound according to claim 12 wherein the fused ring is selected from thiazolo, oxazolo, imidazolo and pyrido.
14. A compound according to claim 13 wherein the fused ring is thiazolo.
15. A compound according to any one of the preceding claims wherein E is selected from O and NH.
16. A compound according to claim 15 wherein E is NH.
17. A compound according to any one of the preceding claims wherein G is selected from hydrogen; monocyclic carbocyclic and heterocyclic groups having 5 or 6 ring members; and acyclic C₁₋₄ hydrocarbyl groups optionally substituted by one or more substituents selected from hydroxy, , halogen, amino, mono- or di-C₁₋₄ hydrocarbylamino, and monocyclic carbocyclic and heterocyclic groups having 5 or 6 ring members; provided that E-G is not OH or SH.
18. A compound according to any one of the preceding claims wherein G is selected from carbocyclic and heterocyclic groups.
19. A compound according to claim 18 wherein G is selected from monocyclic carbocyclic and heterocyclic groups having 5 or 6 ring members.
20. A compound according to claim 18 or claim 19 wherein G is an aryl or heteroaryl group.
21. A compound according to claim 20 wherein the group G is selected from phenyl, naphthyl, pyridyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl,

- tetrazolyl, quinolinyl, isoquinolinyl, benzfuranyl, benzthiophenyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, isobenzofuranyl, isoindolyl, indoliziny, indoliny, isoindoliny, puriny (e.g., adenine, guanine), indazolyl, benzodioxolyl, chromenyl, isochromenyl, isochromanyl, benzodioxanyl, quinoliziny, benzoxazinyl, benzodiaziny, pyridopyridiny, quinoxaliny, quinazoliny, cinnoliny, phthalaziny, naphthyridiny and pteridiny.
- 5 22. A compound according to claim 21 wherein G is selected from phenyl, imidazolyl, pyridyl and isoxazole groups.
- 10 23. A compound according to claim 22 wherein G is a phenyl group.
24. A compound according to claim 18 or claim 19 wherein G is a non-aromatic carbocyclic group such as cyclohexyl or cyclopentyl.
25. A compound according to claim 18 or claim 19 wherein G is a non-aromatic heterocyclic group.
- 15 26. A compound according to claim 25 wherein the non-aromatic heterocyclic group is selected from morpholine, piperidine (e.g. 4-piperidinyl and 3-piperidinyl), pyrrolidine (e.g. 3-pyrrolidinyl and 2-pyrrolidinyl), pyrrolidone, tetrahydrofuran, tetrahydrothiophene, dioxan, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, 20 thiazoline, piperazine, and N-alkyl piperazines such as N-methyl piperazine.
27. A compound according to claim 26 wherein the non-aromatic group is selected from tetrahydropyran, morpholine, piperazine, piperidine and pyrrolidine.
- 25 28. A compound according to any one of the preceding claims wherein G is an unsubstituted carbocyclic or heterocyclic group.

29. A compound according to any one of claims 1 to 27 wherein G is a carbocyclic or heterocyclic group substituted by one or more substituent groups R^{10} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members, and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; R^c is selected from hydrogen and C₁₋₄ hydrocarbyl; and X¹ is O, S or NR^c and X² is =O, =S or =NR^c.
30. A compound according to any one of claims 1 to 16 wherein G is an acyclic C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the acyclic C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$.
31. A compound according to claim 30 wherein the group G is an acyclic C₁₋₈ hydrocarbyl group optionally substituted by one or more carbocyclic and heterocyclic groups having from 3 to 12 ring members.
32. A compound according to claim 31 wherein the said carbocyclic and heterocyclic groups are unsubstituted.

33. A compound according to claim 31 wherein the said carbocyclic and heterocyclic groups are substituted with one or more groups R^{10} as defined in claim 29.
34. A compound according to any one of claims 30 to 33 wherein the optionally substituted acyclic C_{1-8} hydrocarbyl group is a C_{1-6} hydrocarbyl group, e.g. a C_{1-4} hydrocarbyl group such as a C_1 , C_2 or C_3 hydrocarbyl group.
35. A compound according to any one of the preceding claims wherein E-G is any one of the groups set forth in Table 1 herein.
36. A compound of the formula (II):



(II)

wherein

A is a group R^2 or CH_2-R^2 where R^2 is a carbocyclic or heterocyclic group having from 3 to 12 ring members;

B is a bond or an acyclic linker group having a linking chain length of up to 3 atoms selected from C, N, S and O;

R^1 is hydrogen or a group selected from SO_2R^b , $SO_2NR^7R^8$, $CONR^7R^8$, NR^7R^9 and carbocyclic and heterocyclic groups having from 3 to 7 ring members;

R^3 and R^4 together with the carbon atoms to which they are attached form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S;

R^5 and R^6 are the same or different and are each selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C₁₋₄ hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c;

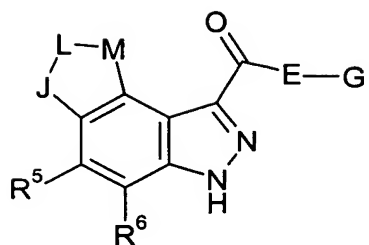
R^7 is selected from hydrogen and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^8 is selected from R^7 and carbocyclic and heterocyclic groups having from 3 to 12 ring members;

R^9 is selected from R^8 , COR⁸ and SO₂R⁸;

or NR⁷R⁸ or NR⁷R⁹ may each form a heterocyclic group having from 5 to 12 ring members.

37. A compound of the formula (III):

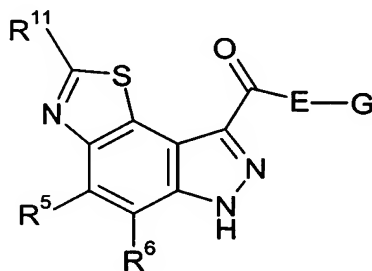


(III)

in which J, L and M are each independently selected from =N-, -S-, -O- and =CR¹¹, R¹¹ is hydrogen or a group R¹⁰ wherein R⁵, R⁶, R¹⁰, E and G are as defined in any one of the preceding claims.

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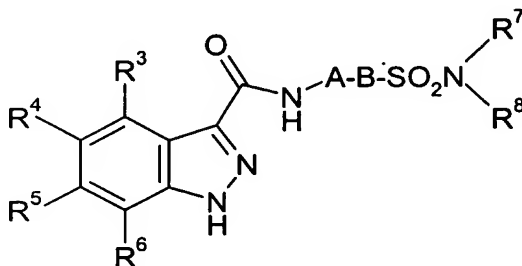
38. A compound according to claim 37 wherein at least one of J, L and M is other than a nitrogen atom.
39. A compound according to claim 37 or claim 38 wherein at least one of J, L and M is =CR¹¹.
- 10 40. A compound according to claim 37 represented by the formula (IV):



(IV)

41. A compound according to claim 40 wherein R⁵ and R⁶ are hydrogen or a small substituent selected from halogen, hydroxy, cyano, methyl, ethyl, trifluoromethyl, or amino.
- 15 42. A compound according to claim 41 wherein wherein R⁵ and R⁶ are hydrogen.

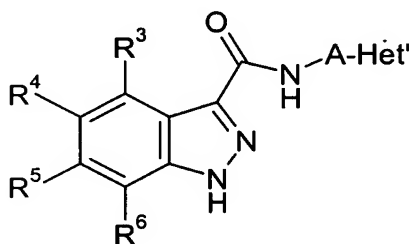
43. A compound according to any one of claims 40 to 42 wherein E-G is any one of the groups A to AI listed in Table 1.
44. A compound according to any one of claims 40 to 43 wherein R¹¹ is selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, amino, mono-C₁₋₄ alkylamino or di-C₁₋₄ alkylamino, carbocyclic and heterocyclic groups having 5 to 7 ring members; and C₁₋₄ hydrocarbyl groups optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, amino, and mono- or di-C₁₋₄ hydrocarbylamino.
45. A compound according to claim 44 wherein R¹¹ is selected from amino, mono-C₁₋₄ alkylamino or di-C₁₋₄ alkylamino, heterocyclic groups having 5 to 6 ring members and containing up to 2 heteroatoms selected from N, O and S; and C₁₋₄ hydrocarbyl groups optionally substituted by one or more substituents selected from hydroxy, halogen, amino, and mono- or di-C₁₋₄ hydrocarbylamino.
46. A compound according to claim 45 wherein R¹¹ is selected from amino, methylamino, ethylamino, cyclopropylamino, methyl, ethyl, hydroxyethyl and pyrrolyl.
47. A compound according to any one of claims 1 and 3 to 35, wherein R⁵ and R⁶ together with the carbon atoms to which they are attached form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S.
48. A compound of the formula (V):



(V)

wherein R^3 to R^8 , A and B are as defined in any one of the preceding claims.

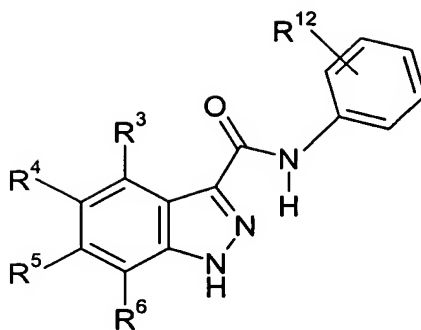
49. A compound according to claim 48 wherein A is a group R^2 wherein R^2 is
 5 an aryl group having six ring members and B is a bond or a methylene group.
50. A compound according to claim 48 or claim 49 wherein R^7 and R^8 are
 selected from hydrogen and C_{1-4} alkyl or R^7 and R^8 together with the
 nitrogen atom form a saturated five or six membered heterocyclic ring
 10 having one or two heteroatoms.
51. A compound according to claim 50 wherein R^7 and R^8 together with the
 nitrogen atom form a saturated heterocyclic ring selected from morpholino,
 piperidino, piperazino and pyrrolidino.
52. A compound according to claim 51 wherein R^7 is hydrogen and R^8 is
 15 hydrogen or methyl.
53. A compound of the formula (VI):



(VI)

- wherein R^3 to R^6 and A are as defined in any one of the preceding claims
 20 and Het' is a heterocyclic group having from 3 to 7 ring members.

54. A compound of the formula (V):

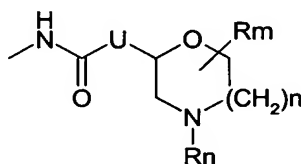


(VII)

wherein R^3 to R^6 are as defined in any one of the preceding claims, and R^{12} represents hydrogen or one or more substituents selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl and trifluoromethoxy.

55. A compound according to claim 54 wherein R^{12} represents hydrogen or one or two fluorine atoms, preferably one fluorine atom.
56. A compound according to any one of the preceding claims wherein when A is R^2 and R^2 is an aryl group having 6 ring members and bearing a C_{1-6} alkyl or halogen substituent in the *para* position, the group $B-R^1$ is other than an unsubstituted or substituted benzamido group located at the *meta* position of the aryl group.
57. A compound according to any one of the preceding claims wherein when A is R^2 and R^2 is an aryl group having 6 ring members, the group $B-R^1$ is other than a substituted phenyl carbamoyl group located at the *meta* position of the aryl group wherein the substituted phenyl carbamoyl group bears a C_{1-6} alkyl or halogen substituent in the *ortho* position and an amido group in the *para* position.
58. A compound according to any one of the preceding claims wherein the fused heterocyclic group, formed by two adjacent moieties selected from R^3 , R^4 , R^5 and R^6 together with the carbon atoms to which they are attached, is other than a 1,2,3-triazolo ring.

59. A compound according to any one of the preceding claims which is other than a compound containing a 3-aminocarbonyl-2-carboxamido-thiophene moiety.
60. A compound according to any one of the preceding claims wherein E is NH and G is an aryl or heteroaryl group selected from five or six membered heteroaryl groups, phenyl, quinoliny and isoquinoliny groups, and the said aryl or heteroaryl group bears a substituent other than C₁₋₆ alkyl, halogen, CF₃, NR^xR^y and OR^z where R^x, R^y and R^z are independently hydrogen, C₁₋₆ alkyl or aryl-C₁₋₆ alkyl.
61. A compound according to any one of the preceding claims wherein the group E-G is not a group of the formula:



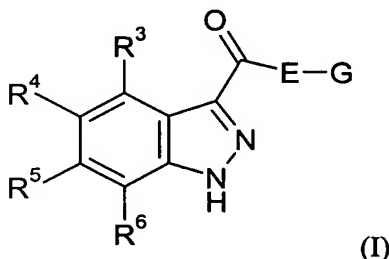
wherein U is an alkylene group, R_m is hydrogen or an alkyl group, R_n is aryl, alkyl or arylalkyl and n is 1 or 2.

62. A compound according to any one of the preceding claims in the form of a salt or solvate (such as a hydrate).
63. A compound according to any one of the preceding claims in the form of an N-oxide.
64. A compound as defined in any one of claims 1 to 63 for use in the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.
65. The use of a compound as defined in any one of claims 1 to 63 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.

66. A method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 63.
- 5 67. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound as defined in any one of claims 1 to 63 in an amount effective in inhibiting abnormal cell growth.
- 10 68. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 63 in an amount effective to inhibit CDK2 activity.
- 15 69. A method of inhibiting a cyclin dependent kinase, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 63.
70. A method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase using a compound as defined in any one of claims 1 to 63.
- 20 71. A pharmaceutical composition comprising a novel compound as defined in any one of claims 1 to 63 and a pharmaceutically acceptable carrier.
72. A compound as defined in any one of claims 1 to 63 for use in medicine.
73. A compound according any one of claims 1 to 63 for use as an antifungal agent.

ABSTRACT**PHARMACEUTICAL COMPOUNDS**

The invention provides a compound of the formula (I):



5 wherein

E is O, S or NH;

G is selected from hydrogen; carbocyclic and heterocyclic groups having from 3 to 12 ring members; and acyclic C₁₋₈ hydrocarbyl groups optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the acyclic C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹; provided that E-G is not OH or SH and further provided that E-G does not contain the group O-O;

two adjacent moieties selected from R³, R⁴, R⁵ and R⁶, together with the carbon atoms to which they are attached, form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S; and the other two moieties selected from R³, R⁴, R⁵ and R⁶ are the same or different and are each selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, X¹C(X²), C(X²)X¹, X¹C(X²)X¹, S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and

a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹;

R^c is hydrogen or C₁₋₄ hydrocarbyl; and

X¹ is O, S or NR^c and X² is =O, =S or =NR^c.

The invention also provides compounds of the formula (I) for use as inhibitors of cyclin dependent kinases and for use in the treatment of disease states and conditions mediated by cyclin dependent kinases.